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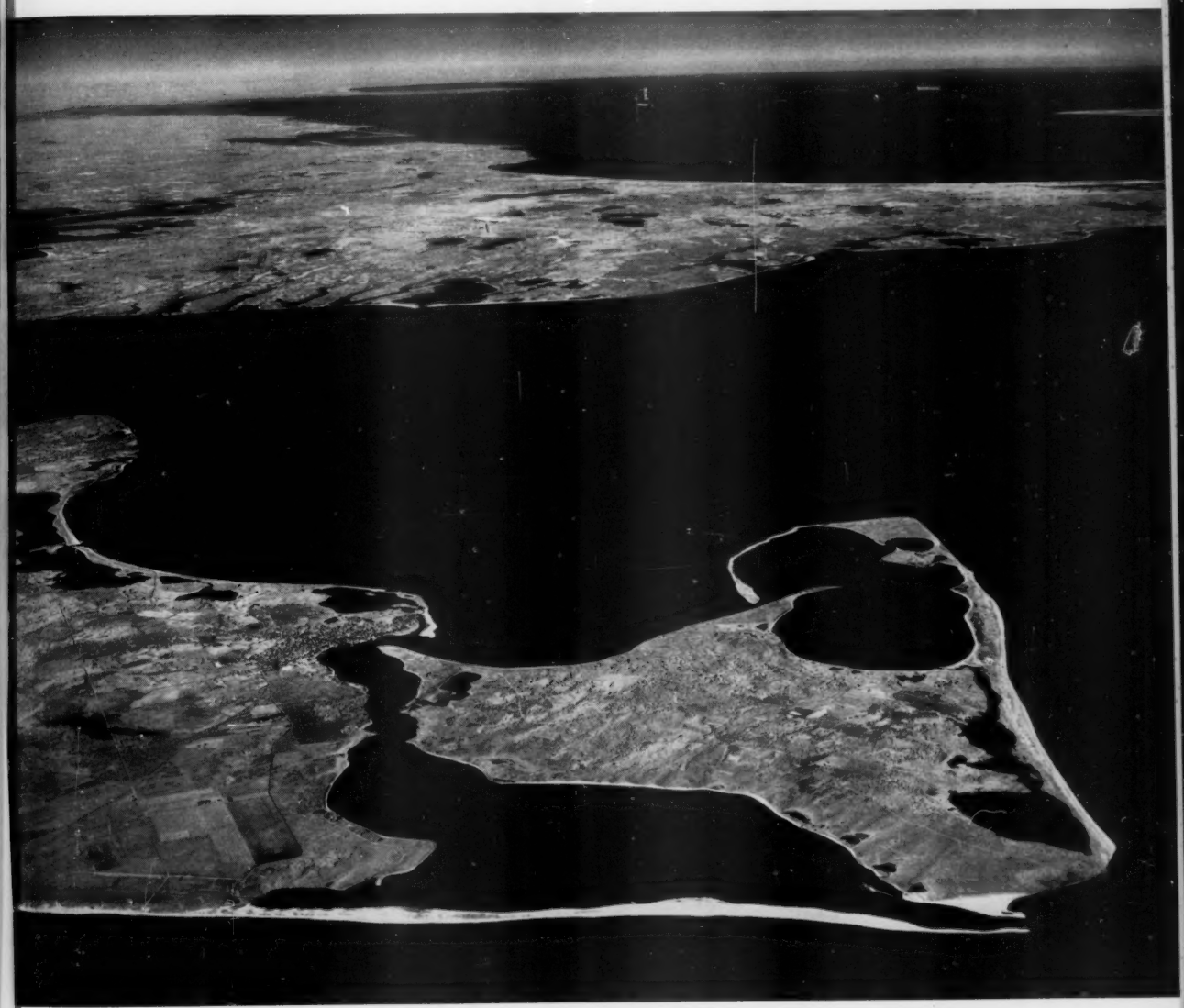

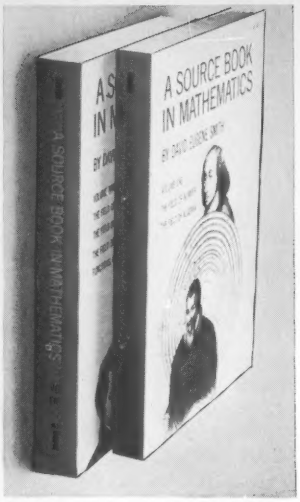

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Letters

Animal Research

As a member of the AAAS I object on moral grounds to those editorial policies which led to the publishing of the article "Effects of differential infantile handling upon weight gain and mortality in the rat and mouse" [*Science* **130**, 629 (1959)] by V. H. Denenberg and G. G. Karas. Their experiments consisted of handling young rodents for various lengths of time and then starving the animals to death. The purpose of this procedure was to determine the stress effects of infantile handling on rats and mice.

In all experiments involving pain or death to animals, (i) the information to be obtained should be worth (in terms of human benefit or real increase in fundamental scientific knowledge) the suffering caused, and (ii) the same or more valuable information should not be obtainable, with a reasonable amount of extra effort, by more humane procedures. These two criteria are practically platitudes.

Since I am not a psychologist I shall not comment on the worth of the experiment. The second criterion given above was not observed and, indeed, the experiment was not only immoral but imprecise. Certainly competent biologists could have suggested tests (anatomical, physiological, biochemical, and so on) for estimating the effect of the stress on the animals that would have provided more precise and interesting data than the one crude fact—how long it took for the animals to starve to death. This more exact information would not have required killing the animals in so cruel and extended a fashion. Note well, it took over 9 days for some of the rats to die. If Denenberg and Karas were not capable of performing these more demanding tests, then they were obligated to ask capable biologists and chemists to assist them, and, of course, to share the authorship of their article.

Very often there is strong pressure exerted on scholars to publish. The editors of *Science* have a moral obligation to see that they do not encourage needlessly painful experimentation by their publishing policies.

R. B. KELMAN

Ossining, New York

The task of selecting an end point, or dependent variable, in research is always a critical one. At times it is a relatively simple matter since, for some problems, an appropriate end point has been established by theory and empirical findings. At other times it is difficult, for a variety of reasons, for an experimenter to arrive at a decision as to which variable or variables to measure. In selecting an end point it is generally agreed by investigators that certain criteria must be met. These criteria include *relevancy*, *sensitivity*, and *precision*. It is obvious that the measured variable must be relevant to the problem under investigation; it must be precise in the sense that it is repeatable; and it must be sensitive enough to detect differences induced by the experimental treatments, if such differences exist. Any variable which satisfies these demands is scientifically valid and may be used to study subhuman organisms. When research is conducted on human beings, other criteria in addition to those listed above must be met.

An end point which has been widely used with animals as a measure of resistance to stress has been survival time after the introduction of some stressor agent. One such stressor has been starvation, either by itself or in combination with other agents. Selye discusses various classes of stimuli including starvation, which act as stressors. The reader is referred to Selye and the other cited literature for further information and references (*1*). Thus, the biological literature definitely establishes that survival time following starvation is a *relevant* dependent variable.

The precision of the survival-time end point has been attested to by the fact that different researchers, working independently, have been able to reproduce one another's results. As was indicated in our paper, Karas and I obtained the same general findings as did two other pairs of researchers. In addition, a partial replication of our data has established the repeatability of the phenomenon. Thus, the survival time measure is a *precise* end point.

The statistical analysis of our data found differences among the various groups well beyond the usually accepted level of significance. These statistical findings have held up in the partial replication. Thus, survival time is a *sensitive* end point.

Since the three criteria specified above have been met, it follows that our measure is scientifically valid and can be used to assess the effects of the experimental treatments.

It may still be argued that the technique is "crude" and that it does not provide "interesting data." With reference to the question of crudeness, it is pertinent to quote here a statement by Selye and Schenker (*1*), who exposed rats to a cold stress under starvation conditions and recorded survival time. In discussing the merits of their technique Selye and Schenker state that "the test is *specific* because it is based upon the preservation of life . . ."

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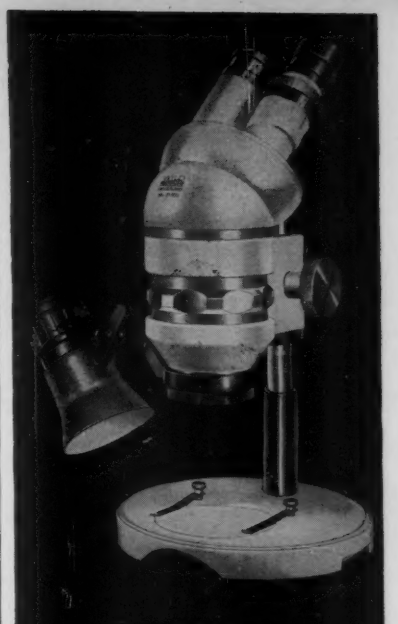

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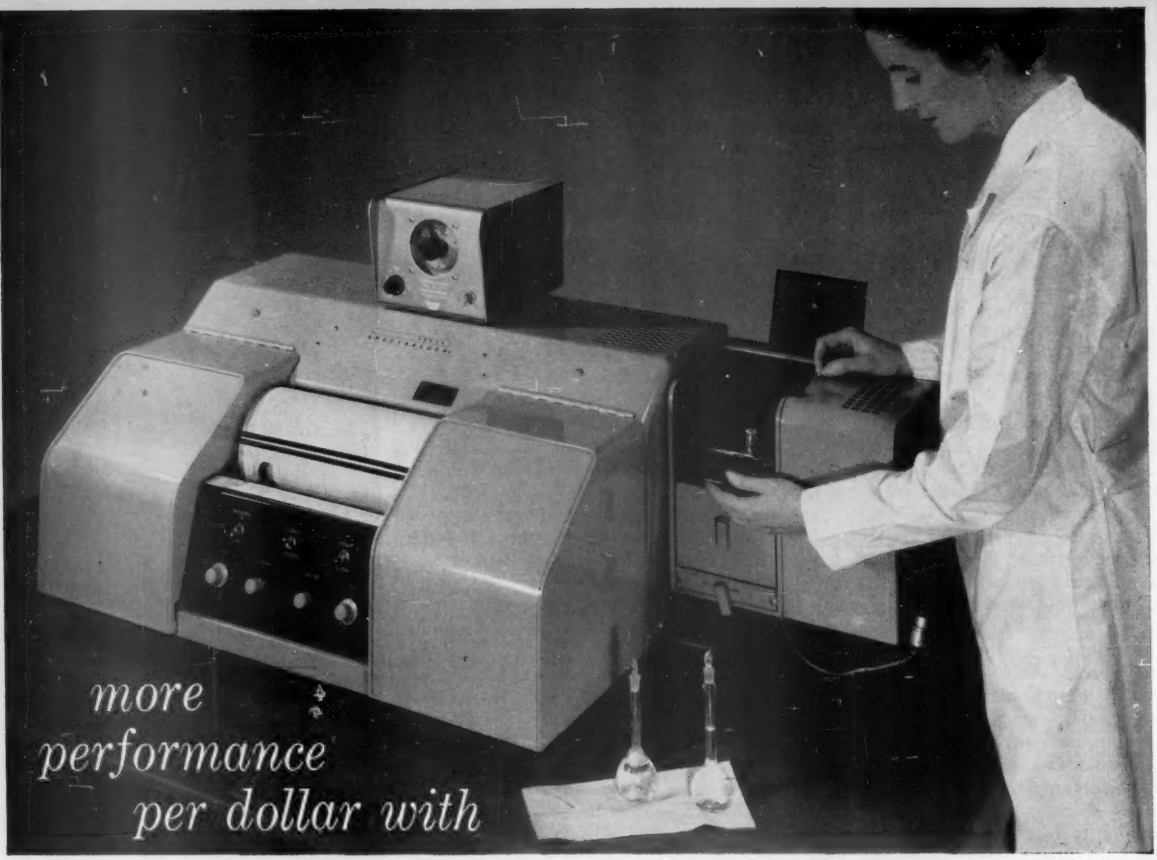

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Cover The Massachusetts coast. Martha's Vineyard is at the lower left, and Chappaquiddick Island is at the right. Nantucket Sound is in the center, and Cape Cod and Massachusetts Bay are in the background. [Photo by Laurence Lowry, from *This Sculptured Earth*, published by Columbia University Press; see page 294]

Letters

(Continued from page 263)

(italics theirs). The question of "interesting" data is one requiring a value judgment which will vary from one researcher to another. Personally, I can think of no datum which is quite as interesting as the length of time an animal can survive under conditions of stress.

The final argument which can be raised against the use of the survival-time technique is that some other measure should be found which will yield "the same or more valuable information." Certainly, if another end point were known which would have permitted us to specify the length of time the animals would live, it would have been used. In fact, all biologists would be studying this end point, for it would be a basic clue to the understanding of life itself. Unfortunately, such an end point is, as yet, unknown.

VICTOR H. DENENBERG
Department of Psychology,
Purdue University, Lafayette, Indiana

Reference

1. The following experimental studies also contain additional references on the same topic: R. I. Dorfman, R. A. Shipley, E. Ross, S. Schiller, B. N. Horwitt, *Endocrinology* **38**, 189 (1946); R. I. Dorfman, R. A. Shipley, S. Schiller, B. N. Horwitt, *ibid.* **38**, 165 (1946); "Shock syndrome," *Ann. N.Y. Acad. Sci.* (1952); H. Selye, *Stress* (Acta, Montreal, 1950); H. Selye and V. Schenker, *Proc. Soc. Exptl. Biol. Med.* **39**, 518 (1938); M. Zarrow, *ibid.* **50**, 135 (1942).

Glaciation and Scientific Terminology

In the interest of public education in science and appreciation of science and scientists, I wish to protest the use of terms with long-established meanings to express concepts totally different. I refer to the use, by Brier and Kline, of the term *glaciation* to mean "formation of crystals . . . in supercooled clouds" [*Science* **130**, 717 (1959)]. For at least three generations *glaciation* has denoted "alternation of the earth's solid surface through erosion and deposition by glacier ice" [R. F. Flint, *Glacial Geology and The Pleistocene Epoch* (Wiley, New York, 1947)].

Millions of our lay public are familiar with this meaning. The study of glaciers and Pleistocene history is vitally significant in archeology and oceanography as well as in meteorology and geology. Communication among these interested groups, and with our supporting public, is jeopardized by the inadvertent introduction of multiple, diverse definitions of common and essential terms. As many geology teachers are discovering, the mischief already done by thoughtless or unwise use of terms is making effective teaching and efficient learning increasingly difficult. The progress and welfare of the newer and less developed scientific disciplines, as well as of the older ones, require care and discretion in using and developing our terminology.

CHAUNCEY D. HOLMES
Department of Geology,
University of Missouri, Columbia

A preliminary search of the meteorological history of the term *glaciation* indicates that the particular usage criticized by Holmes may be a relatively recent revival of this derivative from the Latin word clearly denoting *freezing*. The term is fairly well established (perhaps not irrevocably) in the cloud physicists' vocabulary with reference to the sometimes striking and massive transformation of natural clouds to ice crystals [see, for example, F. H. Ludlam and P. M. Saunders, "Shower formation in large cumulus clouds," *Tellus* **8**, 424 (1956)].

If it is assumed that a term identifying this particular cloud phenomenon is a necessary or logical consequence of the expanding field of cloud physics, usage in this sense seems entirely consistent with a historically proper connotation. Without meaning to disagree with the general thesis of Holmes' communication, we offer the opinion that this example seems to be one where the distinction in the two meanings should be evident from the context in which the term is likely to appear.

GLENN W. BRIER
DWIGHT B. KLINE
Office of Meteorological Research,
United States Weather Bureau,
Washington, D.C.

High-Altitude Observation Techniques

Those of us who work in the upper-atmosphere research field were pleased to find R. C. Staley's article "High-altitude observation techniques" in *Science* [**130**, 845 (1959)], since we feel that *Science* should endeavor to cover as broad a spectrum of scientific knowledge as possible. We were disappointed to find a number of errors in the article and feel that it would have been of greater value had it been written from a more authoritative and well-balanced viewpoint.

F. E. Roach, who was responsible for the exciting discovery that the diffuse light from the upper atmosphere appears in large patches in the night sky, called "airglow cells," is associated with the Central Radio Propagation Laboratory of the National Bureau of Standards and not with the Colorado High Altitude Observatory as stated by Staley. One of the coauthors of the article in which the phenomenon was first reported, E. Tandberg-Hanssen, was associated with the High Altitude Observatory during his stay in America. The existence of airglow cells was deduced from data taken under the National Bureau of Standards' IGY airglow program from the Bureau's Fritz Peak Observatory in the mountains above Boulder.

On page 847 Staley implied that the spectrum of atomic oxygen and sodium, the N_2 ion, molecular oxygen and nitrogen, and the OH radical extended to 10μ in the infrared. The long-wave-length edge of this emission is caused by the OH radical, whose spectrum ends at 4.4μ (the 9-8 vibrational transition). Only thermal emission by polyatomic molecules located lower in the atmosphere exists beyond that wavelength. Also, on page 847, Staley refers to the night airglow emission as originating at altitudes as high as 1000 km. This number came from a paper which has since been refuted. This shows the fallacy of taking data out of context from a table without having a thorough knowledge of the field. The airglow experts now agree that the airglow 6300 emission originates in the F region at heights not greater than 275 km.

It is now generally accepted that the very-low-frequency emissions known as "whistlers" are definitely lightning-originated; this is not just an "apparent" fact, as implied by Staley. On page 845, paragraph 1, a statement is made which implies that soft radiation was detected by balloons up to heights of 50 km. As correctly stated in the third paragraph, balloons can only reach heights of about 42 km. In the next to the last sentence on page 845 it is stated that atmospheric pressures can be found from radio studies of meteor trails. Atmospheric densities can be determined in this manner, but not pressures. Beynon's name is misspelled both in the text and in the reference. At the bottom of page 846 it is stated that ion production at a given height is extremely sensitive to temperature changes. The ion-production rate is only moderately dependent on the temperature because of the density change with variation of temperature. A number of statements in the article are controversial ones which have been taken out of context without proper qualification.

DAVID M. GATES
Central Radio Propagation Laboratory,
National Bureau of Standards,
Boulder, Colorado

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Moment of Truth

I once knew an agency whose top officer used a very effective method with his "governing" board. He placed every proposal he submitted on the agenda for three successive meetings. At the first meeting he would say: "Obviously we need not spend time at this meeting, debating this proposal; for today it is merely being recorded on our schedule for careful review at two later meetings." At the second, he would say: "I think it neither feasible nor necessary to devote any particular attention to this item at this meeting. It has been before you previously, and after all it does not come up for any definitive action until our next meeting." At the third and final meeting he would say: "Now gentlemen, this proposal has, as you all know, been before you for some time. The action requested today is the purely formal one of official approval, merely to complete the record on a proposal which has been before you twice previously, and which I am sure already has your carefully weighed consent. Do I hear a motion?"

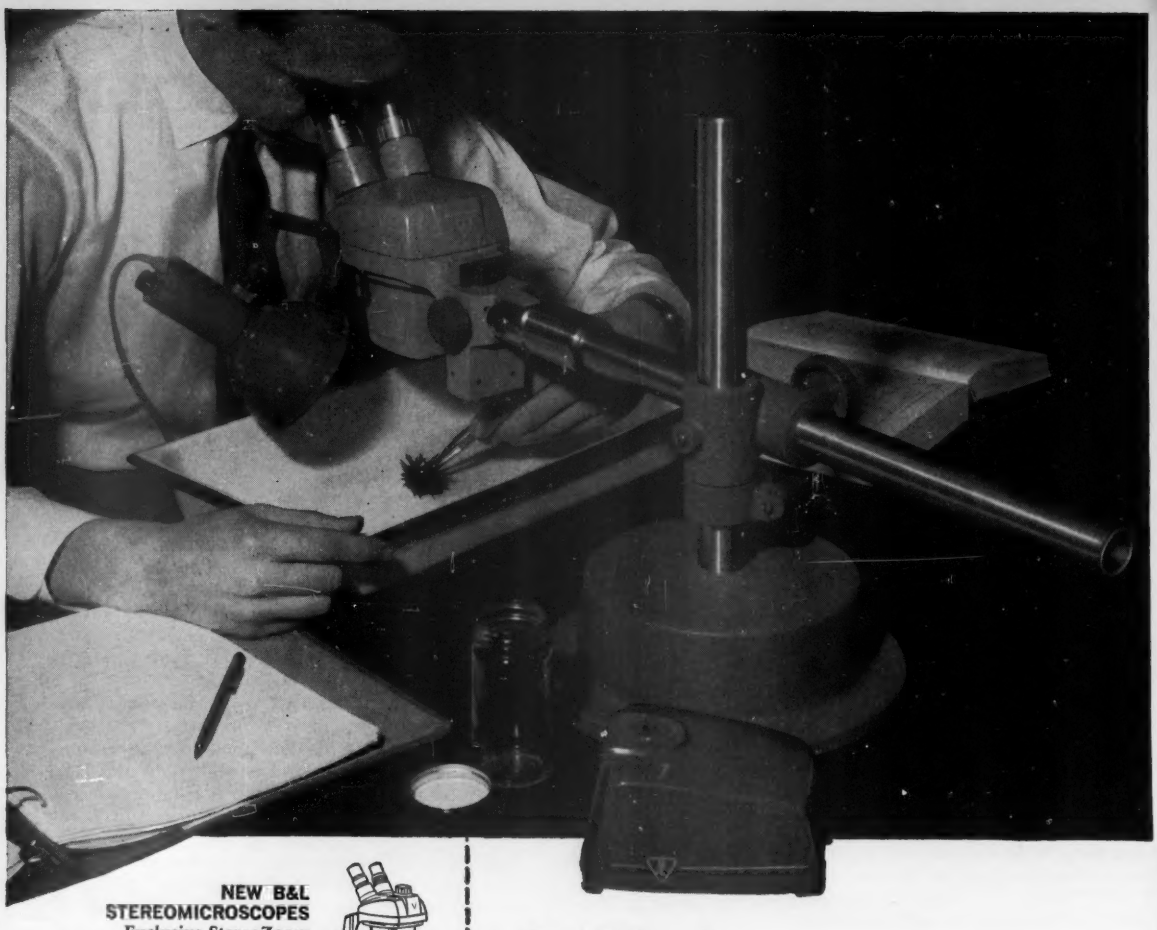
I know another organization that prides itself on the many carefully scheduled steps which constitute the procedure for preliminary approval of any proposal for a new activity. By the time the proposal reaches the higher levels of responsibility, the number of examinations and successive interim approvals is so impressive that there is an almost overwhelming temptation to assume that the real decision has already been made.

I know another organization which approves "preliminary" studies of feasibility, of tentative design, of advance and small-scale laboratory testing of units to see whether they can be made to function—all of this aimed in the direction of some huge new venture. These beginning steps are taken in a rather carefree atmosphere of "Well, it won't cost too much to try out some ideas; and after all, we can decide later whether we really will undertake the huge venture." But presently the organization finds that, without ever facing the central decision, it has drifted into a position from which retreat is impossible.

I hope it will not be too abrupt and curious a change of scene to recall what happens under the warm afternoon sun within the Plaza de Toros in Madrid, or Mexico City, or Linares, or Bogotá, or in many other Latin cities.

At each running of the bulls, after the haunting and foreboding pageantry of the entry; after the mad rush out through the gates of fear; after the grotesque ceremony of the picadores and the stylized precision of the banderilleros; after the exquisite skill and the frenetic bravado of the matador—then comes that quiet instant when best and man face each other in motionless challenge. Then is the moment when the bull's head goes down and the bright blade is poised. Then is the moment when courage and beauty and death confront one another, not in sham play, but in terrifying and noble reality.

If this honest and clear focus of decision can be achieved in the bull ring, is it too much to hope that, in the infinitely more significant contests which decide the great issues of support for science, we can make the preliminary steps serve, but not conceal or dominate? Is it too much to hope that there can be a cleanly recognized, an honestly recognized, moment when courage and wisdom and accepted responsibility confront the act of decision? Is it too much to hope that, in the administrative management of science and in the determining of the major lines of strategy, there occurs, from time to time, a moment of truth?—WARREN WEAVER, *Alfred P. Sloan Foundation, New York*



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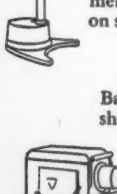

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A View of Genetics

Joshua Lederberg

The Nobel statutes of 1900 charge each prize winner to give a public lecture in Stockholm within six months of Commemoration Day. That I have fully used this margin is not altogether ingenuous, since it furnishes a pleasant occasion to revisit my many friends and colleagues in your beautiful city during its best season.

The charge might call for a historical account of past "studies on genetic recombination and organization of the genetic material in bacteria," studies in which I have enjoyed the companionship of many colleagues, above all my wife. However, this subject has been reviewed regularly (*36-38; 41; 42; 45; 49; 54; 55; 58*), and I hope you will share my own inclination to assume a more speculative task, to look at the context of contemporary science in which bacterial genetics can be better understood, and to scrutinize the future prospects of experimental genetics.

The dispersion of a Nobel award in the field of genetics symbolizes the convergent efforts of a world-wide community of investigators. That genetics should now be recognized is also timely—for its axial role in the conceptual structure of biology, and for its ripening yield for the theory and practice of medicine. However, experimental genetics is reaching its full powers in coalescence with biochemistry: In principle, each phenotype should eventually be denoted as an exact sequence of amino acids in protein (*79*) and the genotype as a corresponding sequence of nucleotides in DNA (*63*). The precise demarcation of genetics from biochemistry is already futile: but when genetics has been fully reduced to its molecular foundations, it may continue to serve in the same relation as thermodynamics to mechanics (*69*). The coordination of so many adjacent sciences will be a cogent challenge to the intellectual powers of our successors.

That bacteria and their genetics should now be so relevant to general biology is already a fresh cycle in our scientific outlook. When thought of at all, they have often been relegated to some obscure byway of evolution, their complexity and their homology with other organisms grossly underrated. "Since Pasteur's startling discoveries of the important role played by microbes in human affairs, microbiology as a science has always suffered from its eminent practical applications. By far the majority of the microbiological studies were undertaken to answer questions connected with the well-being of mankind" (*30*). The pedagogic cleavage of academic biology from medical education has helped sustain this distortion. Happily, the repatriation of bacteria and viruses is only the first measure of the repayment of medicine's debt to biology (*6, 7, 8*).

Comparative biochemistry has consummated the unification of biology revitalized by Darwin one hundred years ago. Throughout the living world we see a common set of structural units—amino acids, coenzymes, nucleins, carbohydrates, and so forth—from which every organism builds itself. The same holds for the fundamental processes of biosynthesis and of energy metabolism. The exceptions to this rule thus command special interest as meaningful tokens of biological individuality, for example, the replacement of cytosine by hydroxymethyl cytosine in the DNA of T2 phage (*12*).

Nutrition has been a special triumph. Bacteria which required no vitamins had seemed simpler than man. But deeper insights (*36, 61*) interpret nutritional simplicity as a greater power of synthesis. The requirements of more exacting organisms comprise just those metabolites they cannot synthesize with their own enzymatic machinery.

Species differ in their nutrition: if species are delimited by their genes, then genes must control the biosynthetic steps which are reflected in nutritional patterns. This syllogism, so evident once told, has been amplified by Beadle and Tatum from this podium. Its implications for experimental biology and medicine are well-known: among these, the methodology of bacterial genetics. Tatum has related how his early experience with bacterial nutrition reinforced the foundations of the biochemical genetics of *Neurospora*. Then, disregarding the common knowledge that bacteria were too simple to have genes, Tatum took courage to look for the genes that would indeed control bacterial nutrition. This conjunction marked the start of my own happy association with him, with the fascinating challenges of bacterial genetics.

Contemporary genetic research is predicated on the role of DNA as the genetic material of enzyme proteins as the cell's working tools and of RNA as the communication channel between them (*63*). Three lines of evidence substantiate the genetic function of DNA. Two are related to bacterial genetics; the third and most general is the cytochemical observation of DNA in the chromosomes, which are undeniably strings of genes. But chromosomes also contain

Dr. Lederberg is professor of genetics at Stanford University Medical School, Palo Alto, Calif. Together with Edward L. Tatum and George W. Beadle, he was awarded the Nobel prize in medicine and physiology for 1958. This article was delivered as a lecture before the Caroline Institute, Stockholm, Sweden, on 29 May 1959. It is published with the permission of the Nobel Foundation. Dr. Tatum's and Dr. Beadle's Nobel lectures appeared in an earlier issue [*Science* **129**, 1711, 1715 (1959)].

other constituents besides DNA: we want a technique to isolate a chromosome or a fragment of one, to analyze it and to retransplant it to verify its functional capacity. The impressive achievements of nuclear transplantation (*29*) should encourage the audacity needed to try such experiments. The constructive equivalent to chromosome transplantation was discovered by a bacteriologist thirty years ago (*20*). The genetic implications of the "pneumococcus transformation" in the minds of some of Griffith's successors were clouded by its involvement with the gummy outer capsule of the bacteria. However, by 1943, Avery and his colleagues had shown that this inherited trait was transmitted from one pneumococcal strain to another by DNA. The general transmission of other traits by the same mechanism (*25*) can only mean that DNA comprises the genes (*94*).

To reinforce this conclusion, Hershey and Chase (*23*) proved that the genetic element of a bacterial virus is also DNA. Infection of a host cell requires the injection of just the DNA content of the adsorbed particle. This DNA controls not only its own replication in the production of new phage but also the specificity of the protein coat, which governs the serological and host range specificity of the intact phage.

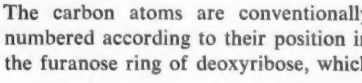
At least in some small viruses, RNA also displays genetic functions. However, the hereditary autonomy of gene-initiated RNA of the cytoplasm is now very doubtful—at least some of the plasmagenes that have been proposed as fulfilling this function are now better understood as feedback-regulated systems of substrate-transport (*65, 72, 81*).

The work of the past decade thus strongly supports the simple doctrine that all genetic information is nucleic, that is, is coded in a linear sequence of nucleotides. This simplification of life may appear too facile, and has furnished a tempting target for agnostic criticism (*37, 41, 44, 74*). But, while no scientific theory would decry continual refinement and amplification, such criticism has little value if it detracts from the evident fruitfulness of the doctrine in experimental design.

The cell may, of course, carry information other than nucleic either in the cytoplasm or, accessory to the polynucleotide sequence, in the chromosomes. Epinucleic information has been invoked, without being more precisely defined, in many recent speculations on cytodifferentiation and on such models of this as antigenic phase variation in *Salmonella* (*47, 52, 56, 71*). Alternative schemes have so much less information capacity than the nucleic cycle that they are more likely to concern the regulation of genic functions than to mimic their specificities.

Deoxyribonucleic Acid as a Substance

The chemistry of DNA deserves to be exposed by apter craftsmen (*13, 31, 86*), and I shall merely recapitulate before addressing myself to its biological implications. A segment of DNA is illustrated in Fig. 1. This shows a linear polymer whose backbone contains the repeating unit:



The carbon atoms are conventionally numbered according to their position in the furanose ring of deoxyribose, which is coupled as an N-glycoside to one of the nucleins: adenine, guanine, cytosine, or thymine, symbolized A, G, C, and T, the now well-known alphabet in which genetic instructions are composed. With a chain length of about 10,000 residues, one molecule of DNA contains 20,000 "bits of information," comparable to the text of this article, or in a page of newsprint.

Pyrophosphate-activated monomer units (for example, thymidine triphosphate) have been identified as the metabolic precursors of DNA (*31*). For genetic replication the monomer units must be assembled in a sequence that reflects that of the parent molecule. A plausible mechanism has been forwarded by Watson and Crick (*87*) as a corollary to their structural model whereby DNA occurs as a two-stranded helix, the bases being centrally oriented. When their relative positions are fixed by the deoxyribose-phosphate backbones, just two pairs of bases are able to form hydrogen bonds between their respective NH and CO groups; these are A:T and G:C. This pairing of bases would tie the two strands together for the length of the helix. In conformity with this model, extensive analytical evidence shows a remarkable equality of A with T and of G with C in DNA from various sources. The two strands of any DNA are then mutually complementary, the A, T, G, and C of one strand being represented by T, A, C, and G, respectively, of the other. The information of one strand is therefore equivalent to, because fully determined by, the other. The determination occurs at the replication of one parent strand by the controlled stepwise accretion of monomers to form a complementary strand. At each step only the monomer which is

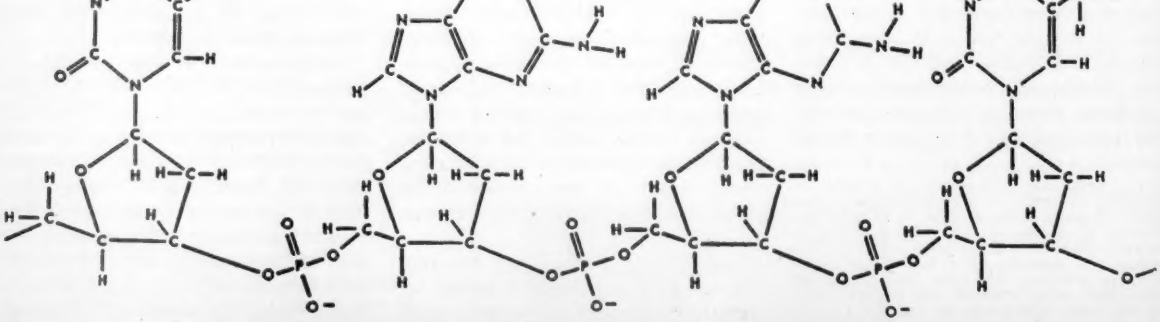


Fig. 1. Primary structure of DNA—a segment of polynucleotide sequence CGGT. [(From *13*)]

complementary to the template would fit for a chain-lengthening esterification with the adjacent nucleotide. The model requires the unraveling of the intertwined helices to allow each of them to serve as a template. This might, however, occur gradually, with the growth of the daughter chain—a concept embedded in Fig. 2, which symbolizes the new Cabala. The discovery of a single-stranded configuration of DNA (*85*) makes complete unraveling more tenable as an alternative model.

For the vehicle of life's continuity, DNA may seem a remarkably undistinguished molecule. Its over-all shape is controlled by the uniform deoxyribose phosphate backbone whose monotony then gives x-ray diffraction patterns of high crystallinity. The nucleins themselves are relatively unreactive, hardly different from one to the other, and in DNA introverted and mutually saturated. Nor are any of the hydroxyls of deoxyribose left unsubstituted in the polymer.

The most plausible function of DNA is ultimately to specify the amino acid sequence in proteins. However, as there are twenty amino acids to choose among, there cannot be a one-to-one correspondence of nucleotide to amino acid. Taking account of the code-duplication in complementary structures and the need to indicate spacing of the words in the code sequence, from three to four nucleins may be needed to spell one amino acid (*19*).

While a protein is also defined by the sequence of its monomeric units, the amino acids, the protein molecule lacks the "aperiodic crystallinity" (*80*) of DNA. The differentiae of the amino acids vary widely in size, shape, and ionic charge (for example, $H^{\cdot}$; $CH_3^{\cdot}$; $H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2^{\cdot}$; $COOH{\cdot}CH_2{\cdot}CH_2^{\cdot}$; $HO{\cdot}C_6H_4{\cdot}CH_2^{\cdot}$) and in the case of proline, bond angles. The biological action of a protein is, therefore, attributable to the shape of the critical surface into which the polypeptide chain folds (*73*). The one-dimensional specificity of the DNA must therefore be translated into the three-dimensional specificity of an enzyme or antibody surface. The simplest assumption would be that the amino acid sequence of the extended polypeptide, as it is released from the protein-building template in the cytoplasm, fully determines the folding pattern of the complete protein, which may, of course, be stabilized by nonpeptide linkages. If not we should have to interpose some accessory mechanism to govern the folding of the protein.

Fig. 2. The scheme of Watson and Crick for DNA replication. "Unwinding and replication proceed *pari passu*. All three arms of the Y rotate as indicated" (*14*).

This issue has reached a climax in speculations about the mechanism of antibody formation. If antibody globulins have a common sequence on which specificity is superimposed by directed folding, an antigen could directly mold the corresponding antibody. However, if sequence determines folding, it should in turn obey nucleic information. As this should be independent of antigenic instruction, we may look instead to a purely selective role of antigens to choose among nucleic alternatives which arise by spontaneous mutation (*8, 50*).

The correspondence between amino acids and clusters of nucleotides has no evident basis in their inherent chemical makeup, and it now appears more probable that this *code* has evolved secondarily and arbitrarily to be translated by some biological intermediary. The coding relationship would then be analogous to, say, Morse-English (binary linear) to Chinese (pictographic). Encouragingly, several workers have reported the enzymatic reaction of amino acids with RNA fragments (*22, 75*). Apparently each amino acid has a different RNA receptor and an enzyme whose twofold specificity thus obviates any direct recognition of amino acid by polynucleotides. The alignment of amino-acyl residues for protein synthesis could then follow controlled assembly of their nucleotidates on an RNA template, by analogy with the model for DNA replication. We then visualize the following modes of information transfer:

1) DNA replication—assembly of complementary deoxyribonucleotides on a DNA template.

2) Transfer to RNA by some comparable mechanism of assembling ribonucleotides. Our understanding of this is limited by uncertainties of the structure of RNA (*16*).

3) Protein synthesis: (i) aminoacylation of polynucleotide fragments; (ii) assembly of the nucleotidates on an RNA template by analogy with step 1; (iii) peptide condensation of the amino acid residues.

Some workers have suggested that RNA is replicated in step 3 concurrently with protein synthesis, in addition to its initiation from RNA.

The chief difference in primary structure between DNA and RNA is the hydroxylation of C'_2 in the ribose, so that a reactive sugar hydroxyl is available in RNA. This may prove to be important in the less ordered secondary structure of RNA, and in its function as an intermediary to protein. It remains to be determined whether the aminoacyl nucleotidates are esterified at C'_2 or at C'_3 which is also available in the terminal residue. From this résumé we may observe that the DNA backbone constitutes an inert but rigid framework on which the differential nucleins are strung. Their spatial constraint lends specificity to the pattern of hydrogen bonding exposed at each level. This extended pattern is a plausible basis for replication; it is difficult to visualize any reagents besides other nucleotides to which this pattern would be relevant. These conditions are quite apt for a memory device—rubber and guncotton are poor choices for a computing tape.

Deoxyribonucleic Acid and Bacterial Mutation

The *ignis fatuus* of genetics has been the specific mutagen, the reagent that would penetrate to a given gene, recognize it, and modify it in a specific way. Directed mutation has long been discredited for higher organisms and the "molar indeterminacy" of mutation established both for its spontaneous occurrence and its enhancement by x-rays (*68*). However, the development of resistance apparently induced by drugs revived illusions that bacterial genes might be alterable, an inference that would inevitably undermine the conception of "gene" for these organisms. No wonder that the mechanism of drug resistance has excited so much controversy (*89*)!

What sort of molecule could func-

tion as a specific mutagen, a reagent for a particular one of the bacterium's complement of genes, which can hardly number less than a thousand targets? On the nucleic hypothesis, the smallest segment capable of this variety would be a *hexa*nucleotide, all possible configurations of which must be discriminated by the specific mutagen. How could this be generally accomplished except by another molecule of conforming length and periodicity, that is an analogous polynucleotide? Certainly there is nothing in the chemistry of penicillin or streptomycin to support their direct intervention in nucleic instructions.

In addition, we recognize no chemical reagent capable of substituting one nuclein for another in the structure of existent DNA. However, as the modification of a nuclein, even to give an unnatural base, could have mutagenic effect, the chief limitation for specific mutagenesis is the recognition of the appropriate target.

Of course the origin of drug resistance, for all its theoretical implications, poses an experimental challenge of its own. Concededly, experiments cannot decide untried situations. Nevertheless, the mechanism whereby resistant mutants arise spontaneously and are then selected by the drug can account for every well-studied case of inherited resistance (*5, 10*). However, in some favorable instances the spontaneous origin of drug-resistant mutants can be verified unambiguously by contriving to isolate them without their ever being exposed to the drug. One method entails indirect selection. To illustrate its application, consider a culture of *Escherichia coli* containing 10^9 bacteria per milliliter. By plating samples on agar containing streptomycin, we infer that one per million bacteria or 10^3 per milliliter produce resistant clones. But to count these clones they were selected in the presence of streptomycin which hypothetically might have induced the resistance. We may, however, dilute the original bacteria in plain broth to give samples containing 10^5 per milliliter. Since 10^{-6} of the bacteria are resistant, each sample has a mathematical expectation of 0.1 of including a resistant bacterium. The individual bacteria being indivisible by dilution, nine samples in ten will include no resistants; the tenth will have one, but now augmented to $1{:}10^5$. Which one this is can be readily determined by retrospective assay on the incubated samples. The procedure can be reiterated to enrich for the resistant organisms until they are obtained in pure culture (*11*). The same result is reached more conveniently if we spread the original culture out on a nutrient agar plate rather than distribute samples into separate test tubes. Replica plating, transposing a pattern of surface growth from plate to plate with a sheet of velvet, takes the place of assaying inocula distributed in tubes (*53*). Dilution sampling and replica plating are then alternative methods of indirect selection whereby the test line is spared direct contact with the drug. Selection is accomplished by saving sublines whose *sibling* clones show the resistant reaction. This proof merely reinforces the incisive arguments that had already been forwarded by many other authors.

If mutations are not specific responses to the cellular environment, how do they arise? We still have very little information on the proximate causes of spontaneous, even of radiation induced and chemically induced, mutation. Most mutagenic chemicals are potent alkylating agents (for example, formaldehyde or nitrogen mustard) which attack a variety of reactive groups in the cell. Similar compounds may occur in normal metabolism and account for part of the spontaneous mutation rate; they may also play a role as chemical intermediates in radiation effects. For the most part, then, studies on mutagenesis, especially by the more vigorous reagents, have told us little about the chemistry of the gene. Probably any agent which can penetrate to the chromosomes and have a localized chemical effect is capable of introducing random errors into the genetic information. If the cell were not first killed by other mechanisms most toxic agents would then probably be mutagenic.

Another class of mutagenic chemicals promises more information: analogs of the natural nucleins which are incorporated into DNA. For example, bromouracil specifically replaces thymine in phage DNA when furnished as bromodeoxyuridine to infected bacteria. Freese has shown, by genetic analyses of the utmost refinement, that the loci of resulting mutations in T4 phage are distributed differently from the mutants of spontaneous origin or those induced by other chemicals (*18*). This method presumably maps the locations of thymine in the original DNA. In order to account for wide variations in mutation rate for different loci, further interactions among the nucleotides must be supposed. So far, these studies represent the closest approach to a rational basis for chemical mutagenesis. However, every gene must present many targets to any nuclein analog, and the specificity of their mutagenesis can be detected only in systems where the resolution of genetic loci approximates the spacing of single nucleotides (*4*). At present this is feasible only in microorganisms; similar studies with bacteria and fungi would be of the greatest interest.

More specific effects might result from the insertion of oligo- and polynucleotides, a program which, however, faces a number of technical difficulties: even if the requisite polymers were to be synthesized, there are obstacles to their penetration into cells. The use of DNA extracted from mutant bacteria to transfer the corresponding genetic qualities is discussed as "genetic transduction."

Ribonucleic acid is the one other reagent that may be expected to recognize particular genes. As yet we have no direct evidence that the transfer of information from DNA to RNA is reversible. However, the antimutagenic effect of nuclein ribosides (*21, 71*) may implicate RNA in mutation. The reversibility of DNA⇆RNA information is also implicit in Stent's closely reasoned scheme for DNA replication (*82*). The needed experiment is the transfer of DNA information by some isolated RNA. Although not reported, this has probably not been fairly tried.

One motivation for this approach is the difficult problem of finding sources of homogeneous nucleic acids. DNA occurs biologically as sets of different molecules presumably in equimolar proportions. [A useful exception may be a remarkably small phage which seems to be unimolecular (*85*).] The species of RNA, however, may vary with the predominant metabolic activity of the cells. If so, some molecular species may be sufficiently exaggerated in specialized cells to facilitate their isolation. A purified RNA would have many potential applications, among others as a vehicle for the recognition of the corresponding DNA implied by our theory of information transfer. Pending such advances, *specific* mutagenesis is an implausible expectation.

Adaptive mutations, of which drug resistance is a familiar example, are crucial to the methodology of microbial genetics. Once having connected adaptive variation with gene mutation (*78*), we could proceed to exploit these systems for the detection of specific geno-

types in very large test populations. The genotypes of interest may arise, as in the previous examples, by mutation: the most extensive studies of the physiology of mutation now use these methods for precise assay. For, in order to count the number of mutants of a given kind, it suffices to plate large numbers of bacteria into selective media and count the surviving colonies which appear after incubation. In this way, mutation rates as low as one per 10^9 divisions can be treated in routine fashion.

Genetic Recombination in Bacteria

The selective isolation of designed genotypes is also the most efficient way to detect genetic recombination. For example, the sexual mechanism of *Escherichia coli* was first exposed when prototrophic (nutritionally self-sufficient) recombinants arose in mixed cultures of two auxotrophic (nutritionally dependent) mutants (*35, 57, 84*). At first only one recombinant appeared per million parental bacteria, and the selective procedure was quite obligatory. Later, more fertile strains were discovered which have been most helpful to further analysis (*45, 51*). This has shown that typical multinucleate vegetative bacteria unite by a conjugation bridge through which part or all of a male genome migrates into the female cell (*43*). The gametic cells then separate. The exconjugant male forms an unaltered clone, surviving by virtue of its remaining nuclei. The exconjugant female generates a mixed clone including recombinants (*1, 46*). Wollman, Jacob, and Hayes (*88*) have since demonstrated that the paternal chromosome migrates during fertilization in an orderly, progressive way. When fertilization is prematurely interrupted, the chromosome may be broken so that only anterior markers appear among the recombinants. All of the genetic markers are arranged in a single linkage group, and their order can be established either by timing their passage during fertilization or by their statistical association with one another among the recombinants. Finally, the transfer of genetic markers can be correlated with the transfer of DNA as inferred from the lethal effect of the radioactive decay of incorporated phosphorus-32 (*27*).

Sexual recombination is one of the methods for analyzing the gene-enzyme relationship. The studies so far are fragmentary, but they support the conception that the gene is a string of nucleotides which must function as a coherent unit in order to produce an active enzyme (*4, 15, 33, 67, 90*). However, metabolic blocks may originate through interference with accessory regulatory mechanisms instead of the fundamental capacity to produce the enzyme. For example, many "lactase-negative" mutants have an altered pattern of enzyme induction or a defective permease system for substrate transport (*55, 65*). Several laboratories are now working to correlate the relative sequence of genetic defects with the sequence of corresponding alterations in enzyme proteins; this may be the next best approach to the coding problem short of a system where a pure DNA can be matched with its protein phenotype.

At first these recombination experiments were confined to a single strain of *Escherichia coli*, K-12. For many purposes this is a favorable choice of material—perhaps the main advantage is the accumulation of a library of many thousands of substrains carrying the various markers called for by the design of genetic tests. However, strain K-12 is rather unsuitable for serological studies, having lost the characteristic surface antigens which are the basis of serological typing. In any event it would be important to know the breeding structure of the group of enteric bacteria. Systematic studies have therefore been made of the interfertility of different strains of bacteria, principally with a convenient tester of the K-12 strain (*39, 93*). About one fourth of the serotype strains of *E. coli* are fertile with strain K-12, and in at least some instances with one another. Whether the remaining three-fourths of strains are completely sterile, or whether they include different, closed, breeding groups (that is, different genetic species) has not been systematically tested, partly because of the preliminary work needed to establish suitable strains.

Escherichia coli K-12 is also interfertile with a number of strains of *Shigella species* (*59*). Finally, although attempted crosses of *Escherichia coli* with many *Salmonella* types and of types of *Salmonella* with one another have usually failed, Baron has demonstrated crosses of *Escherichia coli* with a unique strain of *Salmonella typhimurium* (*3*). This may be especially useful as a means of developing hybrids which can be used to bridge the studies of sexuality in *Escherichia coli* and transduction in *Salmonella*.

Genes and Viruses

Bacteria furnish a unique opportunity to study the genetic relationships with their host cells. Another treasure of strain K-12 was for a time hidden, that it was lysogenic for a bacterophage, λ, which is technically quite favorable for genetic work. In accord with Burnet's early predictions, we had anticipated that the provirus for λ would behave as a genetic unit, but E. M. Lederberg's first crosses were quite startling in their implication that the prophage segregated as a typical chromosomal marker (*34*). This was shown quite unambiguously by the segregation of lysogenicity versus sensitivity from persistent heterozygous cells, a test which bypassed the then controversial details of fertilization. The viability of such heterozygous cells supports the hypothesis that lysogenicity depends in part on the development of a cytoplasmic immunity to the cytopathic effects of infecting phage as a result of the establishment of the prophage in a bacterial chromosome. This picture is also brought out by *zygotic induction* (*26*) whereby the fertilization of a sensitive cell by a prophage-bearing chromosome may provoke the maturation and progressive growth of the phage and the lysis of the complex. On the other hand, the introduction of a sensitive chromosome into a lysogenic bacterium does not result in this induction. The mode of attachment of prophage to its chromosomal site is as unsettled as the general picture of the higher organization of DNA, but most students favor a lateral rather than an axial relationship for the prophage. The isolation of intact chromosomes of bacteria would give a new approach to this question but has so far been inconclusive.

Another infectious particle that has jumped out of our Pandora's box determines the very capacity of *Escherichia coli* to function as a male partner in fertilization (*51*). For lack of a better inspiration, we call this particle "F." Two kinds of male strains are now recognized according to whether the F particle has a chromosomal or a cytoplasmic location. F+ strains, like the original K-12, are highly contagious for F and will rapidly convert populations of female, F− strains in which they are introduced. Hfr males, on the other hand, have a chromosomal localization of the F factor resulting from occasional transpositions in F+ strains. The different localization of the F particle in the

two cases is diagnosed primarily by the behavior of the particle in crosses. In addition, Hirota and Iijima (*24*) found that the F particle could be eliminated from F+ strains by treatment with acridine dyes. Hfr clones are unaffected by acridine orange, but when they revert to the F+ state, as occasionally happens, the F particle again becomes vulnerable to the dye. The accessibility of extrachromosomal F is paralleled by several other examples of plasmid disinfection (reviewed in *40*); perhaps the most notable is the bleaching of green plant cells by streptomycin (*17, 26*). No reagent is known to inactivate F or prophage while bound to the chromosome.

The virus λ and the plasmagene F are analogous in many features (*28, 48*). Their main differences are:

1) *Cytopathogenicity.* A bacterium cannot long tolerate λ in its cytoplasmic state and remain viable. The vegetative λ must promptly reduce itself to a chromosomal state or multiply aggressively and lyse the host bacterium. F has no known cytopathic effect.

2) *Maturation.* Vegetative λ organizes a protein coat and matures into an infective phage particle. F is known only as an intracellular vegetative element; however, the coat of the F+ cell may be analogous to that of the phage.

3) *Transmission.* λ is infective—that is, it forms a free particle which can penetrate susceptible cells. F is transmitted only by cell-to-cell conjugation.

4) *Fixation.* λ has a foreordained site of fixation on the bacterial chromosome; F has been identified at a variety of sites. However, this difference may be illusory. In special situations, F does have preferential sites of fixation (*77*), and generally, translocations of F to different sites are more readily discovered than those of λ would be.

5) *Induction.* Exposure of lysogenic bacteria to small doses of ultraviolet light causes the prophage to initiate a lytic cycle with the appearance first of vegetative, then of mature phage (*62*). Hfr bacteria make no analogous response. However, the kinetics of the reversion, Hfr→F+, has not been carefully studied.

The genetic function of bacteriophages is further exemplified by *transduction* whereby genes are transferred from cell to cell by the intervention of phage particles. In our first studies we concluded that the bacterial genes were adventitiously carried in normal phage particles (*66, 83, 92*). Further studies favor the view that the transducing particle has a normal phage coat but a defective phage nucleus. This correlation has suggested that a gene becomes transducible when a prophage segment is translocated to its vicinity (*2, 9, 60*).

Transduction focuses special attention of the phenomenon of specific pairing of homologous chromosome segments. Howsoever a transduced gene is finally integrated into the bacterial genome, at some stage it must locate the homologous gene in the recipient chromosome. For in transduction, as in sexual recombination, new information is not merely added to the complement: it must also replace the old. This must involve the confrontation of the two homologues prior to the decision which one is to be retained. Synapsis is even more puzzling as between chromosomes whose DNA is in the stabilized double helix and then further contracted by supercoiling. Conceivably gene products rather than DNA are the agency of synaptic pairing.

The integration of a transduced fragment raises further issues (*41*). The competing hypotheses are the physical incorporation of the fragment in the recipient chromosome, or the use of its information when new DNA is replicated. The same issues still confound models of crossing over at meiosis in higher forms; once again the fundamentals of chromosome structure are needed for a resolution.

Virus versus Gene

The homology of gene and virus in their fundamental aspects makes their overt differences even more puzzling. According to the simplest nucleic doctrine, DNA plays no active role in its own replication other than furnishing a useful pattern. Various nucleotide sequences should then be equally replicable. What then distinguishes virus DNA, which replicates itself at the expense of the other pathways of cellular anabolism? For the T-even phages, the presence of the unique glucosylated hydroxymethyl-cytosine furnishes a partial answer (*12*). However, other viruses such as λ display no unique constituents; furthermore, as prophage they replicate coordinately with bacterial DNA. Does the virus have a unique element of structure, either chemical or physical, so far undetected? Or does it instruct its own preferential synthesis by a code for supporting enzymes?

The Creation of Life

The mutualism of DNA, RNA, and proteins as just reviewed is fundamental to all contemporary life. Viruses are simpler as infective particles but must, of course, parasitize the metabolic machinery of the host cell. What would be the least requirements of a primeval organism, the simplest starting point for progressive replication of DNA in terms of presently known or conjectured mechanisms? They include at least: (i) DNA. (ii) The four deoxyribotide pyrophosphates in abundance. (iii) One molecule of the protein, DNA polymerase. (iv) Ribotide phosphates as precursors for RNA. (v) One molecule of the protein RNA polymerase. (vi) A supply of the 20 amino acyl nucleotidates. Failing these, each of the 20 enzymes which catalyze the condensation of an amino acid and corresponding RNA fragments together with sources of these components. (vii) One molecule of the protein aminoacyl-RNA polymerase.

In principle, this formidable list might be reduced to a single polynucleotide polymerized by a single enzyme. However, any scheme for the enzymatic synthesis of nucleic acid calls for the coincidence of a particular nucleic acid and of a particular protein. This is a far more stringent improbability than the sudden emergence of an isolated DNA such as many authors have suggested, so much more so that we must look for alternative solutions to the problem of the origin of life. These are of two kinds. The primeval organism could still be a nucleic cycle if nucleic replication occurs, however imperfectly, without the intervention of protein. The polymerase enzyme, and the transfer of information from nucleic acid to protein, would then be evolved refinements. Alternatively, DNA has evolved from a simpler, spontaneously condensing polymer. The exquisite perfection of DNA makes the second suggestion all the more plausible.

The nucleoprotein cycle is the climax of biochemical evolution. Its antiquity is shown by its adoption by all phyla. Having persisted for about 10^9 years, nucleoprotein may be the most durable feature of this planet's geochemistry.

At the present time, no other self-replicating polymers are known or understood. Nevertheless, the nucleic system illustrates the basic requirements for such a polymer. It must have a rigid periodic structure in which two or more alternative units can be readily

substituted. It must allow for the reversible sorption of specific monomers to the units in its own sequence. Adjacent, sorbed monomers must then condense to form the replica polymer, which must be able to desorb from the template. Primitively, the condensation must be spontaneous but reliable. In DNA, the sorption depends on the hydrogen bonding of nuclein molecules constrained on a rigid helical backbone. This highly specific but subtle design would be difficult to imitate. For the more primitive stages, both of biological evolution and of our own experimental insight, we may prefer to invoke somewhat cruder techniques of complementary attachment. The simplest of these is perhaps the attraction between ionic groups of opposite charge, for example, NH_3^+ and COO^-, which are so prevalent in simple organic compounds. If the ingenuity and craftsmanship so successfully directed at the fabrication of organic polymers for the practical needs of mankind were to be concentrated on the problem of constructing a self-replicating assembly along these lines I predict that the construction of an artificial molecule having the essential function of primitive life would fall within the grasp of our current knowledge of organic chemistry.

Conclusions

The experimental control of cellular genotype is one of the measures of the scope of genetic science. However, nucleic genes will not be readily approached for experimental manipulation except by reagents that mimic them in periodic structure. Specifically induced mutation, if ever accomplished, will then consist of an act of genetic recombination between the target DNA and the controlled information specified by the reagent. Methods for the step-wise analysis and re-assembly of nucleic acids are likely to be perfected in the near future in pace with the accessibility of nucleic acid preparations which are homogenous enough to make their use worth while. For the immediate future, it is likely that the greatest success will attend the use of biological reagents to furnish the selectivity needed to discriminate one among innumerable classes of polynucleotides. Synthetic chemistry is, however, challenged to produce model polymers that can emulate the essential features of genetic systems (*95*).

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94. One might be tempted to write: "One DNA molecule = one gene." However, the quanta of factorial genetics, based on mutation, recombination, and enzymatic function, are all smaller than the DNA unit of molecular weight, $\sim 6 \times 10^8$ (*4*). There is increasing evidence that such a molecule is a natural unit rather than an artifact of fragmentation (*64*).
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Human and Amphibian Neoplasms Compared

Tumors in frogs and human beings are strikingly similar in cytological characteristics.

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The basic etiology of human tumors is not known and is not readily approachable experimentally. Some understanding of this important problem may be attained, however, by comparing neoplasms in human beings with those in experimental animals. Conferences between us have led to detailed comparison of cytological features from several widely divergent clinical neoplasms. The nuclear and nucleolar characteristics of these tumors are so strikingly similar as to be remarkable. Of possible etiological significance in the human being is the extremely close resemblance to the sequence of events observable in filtrate-induced renal cancers of the frog (*1*). In 1936 Lucké (*2*) noted strong similarities between neoplastic lesions in frog and human kidneys. For the frog he proposed a theory of tumor origin based on a transmissible organ-specific virus. This theory was confirmed and extended by Duryee (*3*) in 1956, using filtrates of homogenized tumors injected directly into host kidneys. A general sequence of nuclear events was observed in the treated kidney and was found to correspond in all details to those of transforming tubules in spontaneous tumor growth, as studied in histological section. Further experimental confirmation was made by exposing normal tubules to sources of virus in tissue cultures (*4*). The following observations on human tumors are of sufficient interest to be presented as isolated, although related, cases. Further research in the next few years will amply confirm or deny the implications of our observations; obviously much work needs to be done.

Amphibian Adenocarcinoma

As background for our comparisons, a brief summary of earlier experimental conclusions is presented. In the amphibian, a physiological sequence of nuclear events followed direct renal injection of tumor filtrate.

1) Simultaneous appearance of "new" deoxyribonucleic acid (Feulgen-positive) particles (presumably virus ag-

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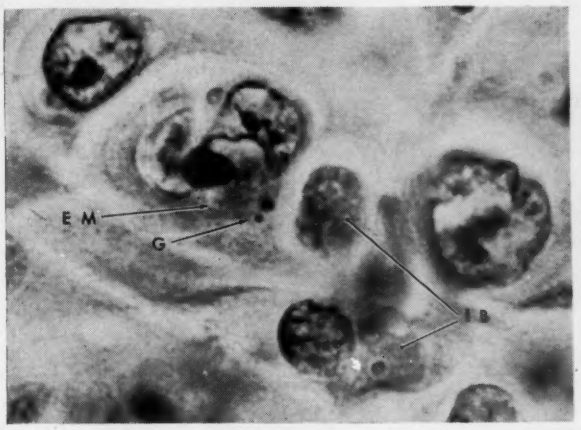
gregates) on the nucleolar surface near the chromosomal attachment point in a high proportion of proximal tubule cells.

2) Hyperactivity of the nucleolar machinery shown by increase in the ribonucleic acid mass of the nucleolus. Great variability between the cells was assumed to reflect different stages in a cyclical process. Eosinophilic intranuclear inclusions were *not* virus aggregates, as described by Lucké, but were simply greatly enlarged nucleolar cores that contained ribonucleic acid.

3) Extrusion of nucleolar ribonucleic acid and deoxyribonucleic acid into the nucleoplasm and thence into the cytoplasm, or directly through the nuclear membrane into the cytoplasm to form ribonucleic-acid-rich cytoplasmic inclusion bodies and occasional granules of aggregated deoxyribonucleic acid particles. The ribonucleic acid inclusion bodies slowly dissolved into the cytoplasm, acting as possible templates for new protein.

Parallel Phenomena in the Human Being

In ovarian carcinoma Taylor and Long (*5*) have noted increases in nucleolar size in highly malignant grade III tumors over that in benign tumors and in tumors of a lower histological grade of malignancy. Nuclei of grade III tumors showed extreme nucleolar hyperactivity and stages in extrusion of nucleolar ribonucleic acid into the cytoplasm. Similar nucleolar ribonucleic



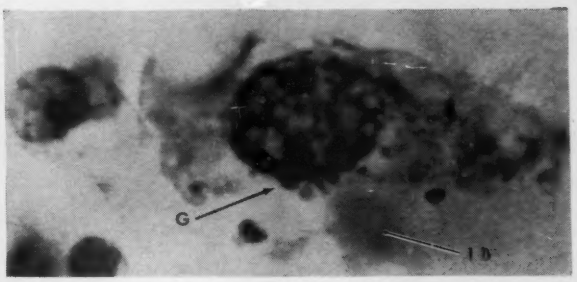
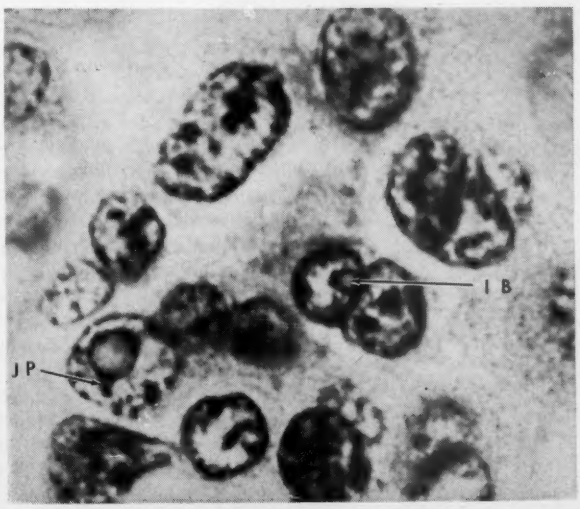


Fig. 1 (left). Human epidermoid cervical carcinoma (10384, M.H.), showing nuclei of highly malignant tumor cells with large eosinophilic inclusion bodies (*IB*) in the cytoplasm. Note the escape of eosinophilic material (*EM*) from the nucleus together with basophilic granules (*G*). Nucleolar hyperactivity is evident in the adjoining cells. (Oil immersion; hematoxylin-eosin.) (About × 1730) [College of Physicians and Surgeons, Columbia University] Fig. 2 (right). Human endometrial carcinoma, grade 3 (59-673, R.S.) in an ascites fluid smear preparation. The large arrow indicates extrusion of deoxyribonucleic acid material (*G*) from the nucleus. A pyronin-positive ribonucleic-acid-rich inclusion body (*IB*) is visible in the adjacent cytoplasm. (Oil immersion; methyl green pyronin Y.) (About × 1730) [College of Physicians and Surgeons, Columbia University]



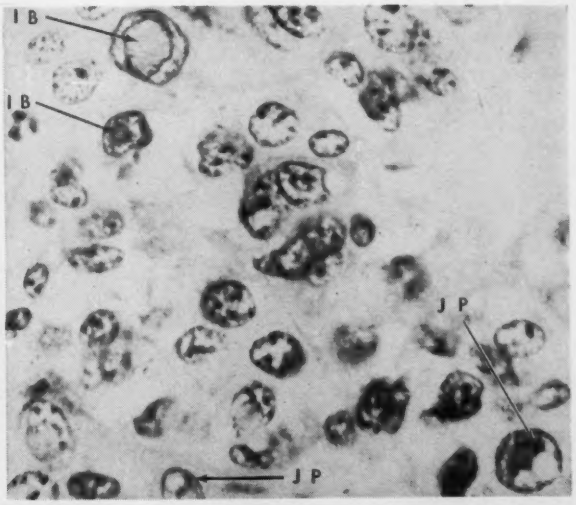


Fig. 3 (left). Human renal adenocarcinoma, grade 1 (S-59-571, M.M). Note the stages in the development of intranuclear eosinophilic inclusion bodies (*IB*) which are developed within the nucleolus and the enlarged nucleolar-chromosomal junction point (*JP*). Nucleolar hyperactivity is evident in several nuclei. (Oil immersion; hematoxylin-eosin.) (About × 1870) Fig. 4 (right). Lower magnification of human renal adenocarcinoma (from the same slide as Fig. 3). Note the large eosinophilic inclusion bodies developing inside the nucleoli (*IB*). The nucleolar chromosomal attachment point is visible in several nuclei (for example, *JP*). (Oil immersion; hematoxylin-eosin.) (About × 800) [Free Hospital for Women, Brookline, Mass.]

acid phenomena have been observed by these investigators in endometrial carcinoma (*6*) and in cervical epidermoid carcinoma (7). Kopac and Mateyko have confirmed and extended these observations in tissue culture studies of ovarian carcinoma (*8*).

Recent studies of Feulgen-reacted gynecological material have shown localization of deoxyribonucleic-acid aggregates around the sites of nucleolar-chromosomal junction points and the presence of minute deoxyribonucleic-acid compounds in cytoplasm. As in amphibian renal adenocarcinoma, such activity was limited to scattered foci within each tumor and was observed predominantly in tumors of the highest grade of malignancy (Figs. 1 and 2).

Localized nests of cells in a 2100-gram adenocarcinoma of the kidney were found to contain all stages of enlarged eosinophilic inclusions in the nucleus, up to 11 microns in diameter. Many examples of intranuclear eosinophilic material containing presumable ribonucleic acid were observed in such areas escaping into the cytoplasm. Occasional cytoplasmic deoxyribonucleic acid granules (0.5 to 1.5 μ) could be identified. The unusual characteristics of these cells deserve attention and suggest that further search of other renal tumors be made, beyond the preliminary exploration which has yielded a small number of comparable cases (Figs. 3 and 4).

In another patient with a presumably benign hydatidiform mole (Hertig group II), focal groups of cells were found showing all stages of enlarged nuclei (up to 25 μ) with large eosinophilic intranuclear masses (up to 18 μ). Stages of massive nucleolar ribonucleic acid escaping into the cytoplasm were observed. It is of interest that no cytoplasmic deoxyribonucleic acid was demonstrable.

In a case of grade I adenocarcinoma of the large intestine, a Feulgen-stained section showed packed nuclei, highly variable in size, with indications of marked nucleolar hyperactivity. There were many examples of intranuclear ribonucleic-acid inclusions and some "new" deoxyribonucleic acid granules. An average of two mitoses per high-power field indicated rapid growth rate. It is of interest that inclusions containing deoxyribonucleic acid were also noted on occasion in the cytoplasm of closely adjacent colon gland cells (Fig. 5). The latter cells of the colon wall illustrate large Feulgen-positive inclusions (2 to 3 μ) in the cytoplasm similar to those noted by Helwig (*9*) and others.

Another case of primary ovarian adenocarcinoma yielded exceptionally clear examples of tumor nodules with Feulgen-positive bodies situated inside and outside the nuclear membrane (Fig. 6).

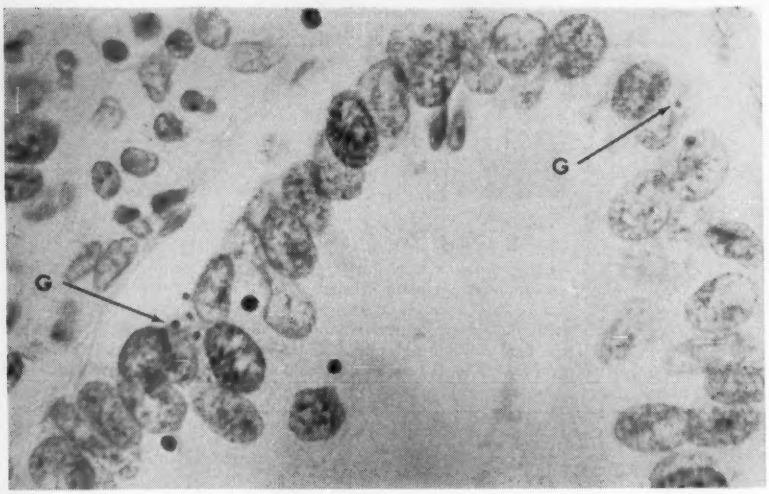


Fig. 5. Early cellular changes in a human colon gland closely adjacent to adenocarcinoma, grade 1 (G-7923, F.D.). Deoxyribonucleic acid granules (*G*) are extruded from the nuclei. (Oil immersion; Feulgen–fast green FCF.) (About × 900) [George Washington University Hospital]

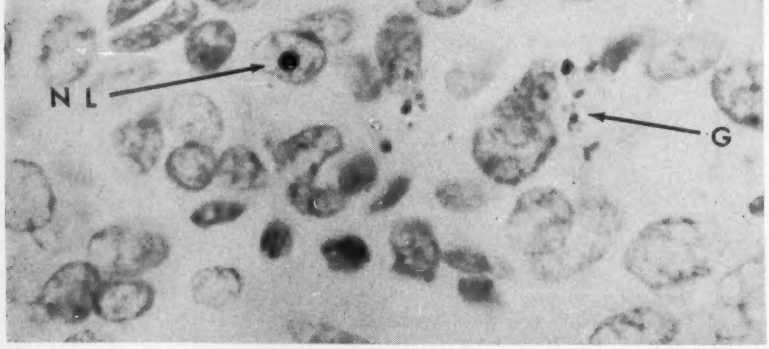
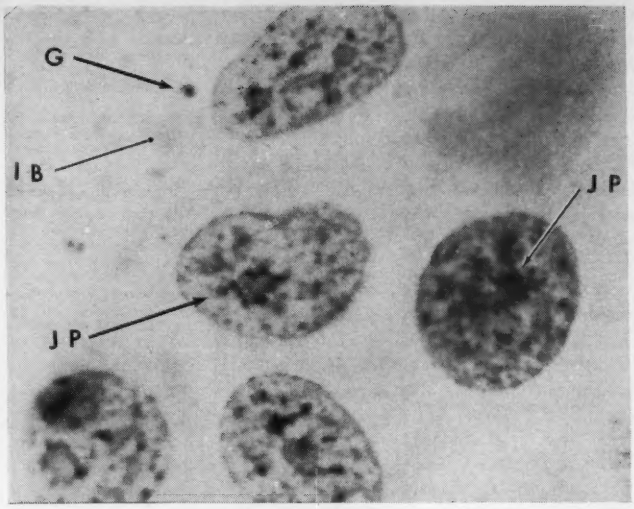


Fig. 6. Human pseudomucinous adenocarcinoma of the ovary, grade 1 (H-76, M.K.). Granules containing deoxyribonucleic acid (*G*) may be seen escaping from nuclei together with a small amount of ribonucleic acid. A hyperactive nucleolus (*NL*) has a Feulgen-positive capsule. (Oil immersion; Feulgen–fast green FCF.) (About × 1160) [George Washington University Hospital]

Spontaneous and Experimental Amphibian Tumors

In comparable ways spontaneous and virus-induced amphibian renal adenocarcinomas agreed in showing deoxyribonucleic acid granules from the nucleus escaping into the cytoplasm. Sections of spontaneous and experimental frog tumors demonstrated clearly that acini of primary renal adenocarcinoma were derived directly from transformed kidney tubules. In the majority of over a hundred cases studied, numerous tubules per kidney were involved, giving clear proof of the multicentric origin of this tumor. Close examination of transforming tubules frequently showed great numbers of infected nuclei with "new" deoxyribonucleic acid granules around the nucleolus. Release of ribonucleic acid from the nucleus allowed the deoxyri-



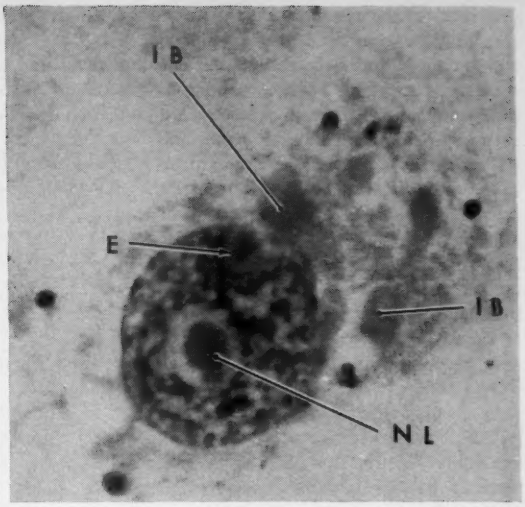


Fig. 7 (left). Frog renal adenocarcinoma nuclei in tissue culture. The arrows indicate a deoxyribonucleic acid granule (*G*) outside of the nucleus; a ribonucleic acid cytoplasmic inclusion body (*IB*) in the cytoplasm; and a hyperactive nucleolus developing at the nucleolar-chromosomal junction point (*JP*), together with additional deoxyribonucleic acid. (Oil immersion; Feulgen–fast green FCF.) (About × 2100) Fig. 8 (right). Frog adenocarcinoma cell nucleus in tissue culture. Note the ribonucleic acid inclusion bodies in the cytoplasm (*IB*), one escaping from the nucleus (*E*), and the ribonucleic acid in the enlarged core of the nucleolus (*NL*). (Oil immersion; Feulgen–fast green FCF.) (About × 2700) [George Washington University School of Medicine]

bonucleic acid granules (presumably virus) to escape also. Strong evidence for the transformation of normal tubules into malignant tissue immediately adjacent to active tumor masses was noted (see Figs. 7–9).

Conclusions

As indicated in the opening statement, histological and cytological features common to all of these human malignant tumors are (i) marked increase in Feulgen-positive granules (deoxyribonucleic acid) around the nucleolus; (ii) increase in the size, and evidence of extreme hyperactivity of the nucleolar machinery, leading to greater than normal extrusion of ribonucleic acid into the nucleoplasm and cytoplasm; (iii) resultant accumulation of nucleolar ribonucleic-acid and occasional deoxyribonucleic acid aggregates in cytoplasm. (Occasional massive cytoplasmic ribonucleic acid inclusion bodies and small "bursts" of deoxyribonucleic acid into extracellular areas are characteristic only of the most malignant grades.)

These findings are compatible with and extend the "cytogenetic" virus concept of Furth (*10*). There is clear evidence that the genetic machinery of an amphibian cell [that is, the deoxyribonucleic acid templates (*11*) of a gene locus on a chromosome] not only can organize nucleolar ribonucleic acid but, under unusual stimulus, can fragment itself (*3, 4*). Stimulation of normal nucleolar machinery of the cell to a highly abnormal or malignant degree by a cytogenetic infecting virus (*10*) is evident in various animal tumors and is consistent with previous, poorly understood, observations on human tumors. The purpose of this article has been to emphasize that these essential features may be experimentally ap-

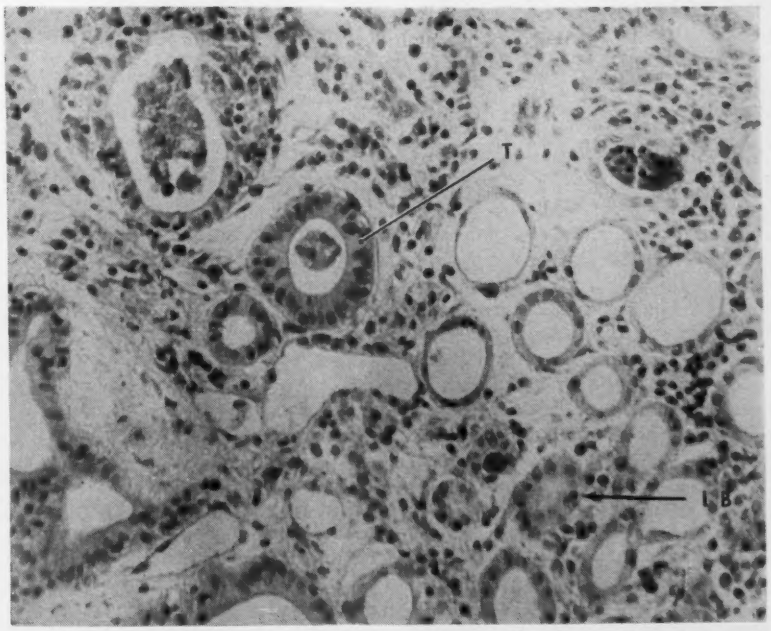


Fig. 9. Section of spontaneous adenocarcinoma of frog kidney showing transforming tubule (*T*). Note the eosinophilic inclusion body (*IB*) in the cytoplasm in another tubule. (Hematoxylin-eosin.) (About × 230) [George Washington University School of Medicine]

proached in the test animal and therefore may be compared with malignant cytology in human beings. A parallelism may throw light on possible conditions of carcinogenesis in human beings, but certainly parallelisms are no proof, and no direct implication that human tumors are virus-induced is allowed or intended. However, it is noteworthy that all the foregoing details in stained frog-kidney sections may be observed in comparable living cell nuclei in tissue culture under the highest powers of phase-contrast microscopy, and it may be pointed out that tissue-cultures of human malignant cells have, in many instances, exhibited nucleolar abnormalities identical with those described in this preliminary presentation (*12*).

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12. The experimental portion of the work on amphibian material was supported by funds from the U.S. Public Health Service (C-2754) and the Damon Runyon Memorial Fund (DRG-437) and by a grant from Mr. and Mrs. Robert B. Flint. The studies of tumors in human beings carried out at Columbia University were supported in part by grants from the Damon Runyon Fund (DRG-413) and from the National Cancer Institute, Bethesda, Md. (C-2428).

Introducing Modern Medicine in a Navajo Community

Physicians and anthropologists are cooperating in this study of changing patterns of culture and disease. The second of two parts.

Walsh McDermott, Kurt Deuschle, John Adair, Hugh Fulmer, Bernice Loughlin

In part I of this article (see last week's issue of *Science*) were presented the background, the goals, and certain of the preliminary findings of a joint medical-anthropologic research program on cross-cultural technologic development in the field of health. The studies are being conducted with the cooperation of the Navajo Tribe and the U.S. Public Health Service in an 800-square-mile area situated in the approximate center of the Navajo land in the southwestern United States.

Few better illustrations of the significance of cross-cultural matters in medicine can be cited from the present study than the situation observed with respect to congenital dislocation of the hip. Indeed the experience has been an excellent lesson in the basic principle that what constitutes a "disease" in one culture does not necessarily constitute a "disease" in another culture.

The authors are affiliated with the Department of Public Health and Preventive Medicine of the New York Hospital–Cornell University Medical Center, New York, N.Y. Miss Loughlin is also affiliated with the School of Nursing. This article is adapted in part from the Edward Jenner memorial lecture delivered by Dr. McDermott at St. George's Hospital Medical College, London, 1 July 1958.

"Congenital" Hip

As had been expected, the prevalence of congenital dislocation of the hip at Manyfarms-Rough Rock was found to be quite high. Indeed the number of cases found represents a prevalence rate of 1090 persons afflicted per 100,000 population, in contrast to a rate of 3.8 persons per 100,000 in New York City. To what extent this disease is truly hereditary has never been precisely established, although it is generally designated as a congenital disorder. It has also been strongly suspected that cultural factors, notably the use of cradleboards, contribute substantially either to the condition itself or to the degree of permanent disability resulting from it. For, on the cradleboard, the infant is securely laced with the outstretched legs bound together in a position that does not favor continued insertion of the head of the femur in the pelvic joint.

Irrespective of the relative roles of genes and culture in causation, there is an increasing body of evidence that the major portion of the disability in congenital hip disease can be prevented if the condition is discovered and appropriate nonsurgical treatment is started during the first year, or at most the first two years, of life. During the next two years (ages three and four), the only satisfactory treatment is surgical and consists of exposing the joint and inserting the femur in its proper location. Once the child has attained the age of five or six years (school age), the only treatments available are the more elaborate surgical procedures of attempting to create a "shelf" of bone, or, if this fails, fusing the hip joint. The latter operation is seldom employed as the initial treatment unless the child has reached the age of 12 or 13 years, and the operation results in a completely stiff and "frozen" hip joint. The reason for purposely producing the obvious physical handicap of a completely fused hip joint is that unless this is done, the patient runs a considerable risk of having a chronically painful traumatic arthritis of the hip when he or she attains the age of 40 or 45.

When in the course of the research program the time seemed appropriate to begin a special study of congenital hip disease, it became abundantly clear from the reactions of the Navajo staff that a highly "tender" area was being approached. Contrary to the immediate assumption, moreover, it speedily became clear that the delicate nature of the matter was quite unrelated to its obvious familial connotations. Something quite different was at issue—namely, that in Navajo culture congenital dislocation of the hip, even when bilateral, is not viewed as a disease or even as a particularly important disability. Boys with this condition are not generally mocked, and girls who have it have no difficulty in obtaining husbands and raising families. Indeed, the fact that one child in a family has congenital hip disease appears to be regarded, not quite as a positive blessing, but as a sort of continuously visible relative blessing. By this is meant a blessing in the sense that when evil struck the family, this was the worst it could do, and evil is not apt to strike one family on too many occasions.

What made the issue such a delicate one was the fact that a number of years previously the members of our Navajo staff had happened to witness the consequences of the surgical treatment of congenital hip in older children in their own homes. As explained above, when congenital hip disease is not discovered until the child has passed a certain age, surgical fusion may be all that can be done. Moreover, this procedure is a perfectly sensible one for an older child or adolescent in the non-Indian culture of the United States. The stiff hip does not prevent the child from getting around, and the risk of a more serious handicap in mid-adult life is prevented. With a Navajo child whose hip joint is fused, however, the situation is completely different. Life around a hogan is enormously complicated for one with a stiff hip. For example, such a person cannot join the family for meals because the whole family usually sits on the ground or on sheepskins at mealtime. Moreover, such a child is unable to ride horseback. In Navajo eyes, these are present realities that cannot be effectively offset by the thought that some other disability, not too well understood, will not be present 20 or 30 years hence.

From the viewpoint of the Navajo staff, therefore, the sole contribution of modern medicine to the question of congenital hip disease was to transform something that was no real handicap, and was almost a blessing, into something that represented a very serious handicap indeed. Once it became clear what was bothering the staff, it was possible to design a study with the initial object of developing ways to identify congenital hip disease sufficiently early in life so that nonsurgical treatment might be applied. A genealogic study of the occurrence of congenital hip disease has been started, with the thought that, if it could be established that the condition is genetically determined, the use of diagnostic x-ray could be limited to infants in families that had a history of hip disease. Although this study is only in its early stages, there appears to be no cultural problem at all with respect to asking questions about antecedents, because kinship relations are matters of considerable interest in Navajo society.

This episode is cited because it illustrates the danger in attempting to build a health program on the illusory concept that health is the absence of disease. In reality, "health" is a relative matter and signifies the degree to which a person can operate effectively within the particular circumstances of his heredity *and environment*. The wisdom of our Navajo staff on this point undoubtedly saved us from considerable difficulty.

From this study of the disease pattern of the community certain general findings appear significant. First, the virtual absence of most of the diseases that are fatal in non-Indian society in the United States serves to emphasize the fact that in reality all societies are disease-ridden; it is only in the disease pattern that the great differences lie (*1*). In economically underdeveloped areas such as the Navajo country, the disease pattern is one of high infant mortality, juvenile invalidism, and premature death, in contrast to the disease pattern in the non-Indian part of the United States, which permits many decades of productive life. Second, in the Manyfarms-Rough Rock community, microbial diseases or their consequences constituted more than three-quarters of the disease found. For most of the diseases, and for virtually all of the fatal ones, effective and practicable measures for treatment or prevention exist. Third, more than 97 percent of the illness encountered could be quite properly and effectively treated in the field clinic facility. Fourth, in such a society, a health program based on the school children is largely a "repair the damage" program.

By the time the child arrives at school at five or six years of age, much of what is going to happen has already

Aerial view of the headquarters of the Field Health Research Project, which is situated on tribal property at Manyfarms, Arizona. The clinic facility and research laboratories are in the white-roofed building at lower right. The living quarters for the staff (left and center) consist of trailers and modified railroad refrigerator cars. The latter were hauled overland 125 miles from the nearest railroad. The building at upper left is a shed for storage of road-maintenance equipment, and the buildings and trailers at upper right form the Manyfarms day school (grades 1 through 3). Many members of the project community reside on top of the mesa seen in the background. [James Bosch, Window Rock, Ariz.]

A Navajo Health Visitor administering penicillin in the field clinic. The Health Visitors are trained to perform certain nursing procedures, such as intramuscular injection of drugs, both in the clinic and in the hogan, thereby freeing the public health nurse for other activities. No medication can be given without a specific prescription by a physician, but in emergencies in the hogan the Health Visitor can obtain such a prescription by means of the radio-telephone with which each automobile is equipped. [American Museum of Natural History]

happened, and he is a "veteran" of human disease. He may be infected with tubercle bacilli, may be deaf from streptococcal infections of the ear, may have some visual difficulties because of trachoma, and may have been walking since infancy with a congenitally dislocated hip. Obviously, therefore, a program in *preventive* medicine, to be fully effective, must be inaugurated with the preschool children. In a society in which the people live in compact villages, the preschool children are relatively accessible. In a society such as the Navajo, with its vast distances between homes, a considerably greater effort in required, in terms of staff and facilities, to organize a health program for preschool children than to organize such a program for any other age group.

"Health Visitors"

The third of the three general studies undertaken by the medical-anthropologic research group has to do with determining to what extent only partially educated Navajo men and women can be trained to function as effective field auxiliaries of the public health nurses. This program is designated the "Health Visitor" program. In a very real sense this program in medical and nursing research represents an attempt to study certain of the implications of the technologic revolution represented by the development of powerful and simply administered antimicrobial drugs.

In conditions such as those that obtain in the Navajo country, where the population is thinly dispersed over the rugged terrain, it is quite difficult for a trained public health nurse to make more than one or two home visits per day. Moreover, she must be accompanied by a driver-interpreter. Obviously no proper field program could be set up until some way could be found to multiply the effectivness of the highly trained public health nurse. An essential feature of the study under discussion is the concept of a *single* all-purpose subprofessional worker—that is, an auxiliary to the field nurse, a driver-interpreter, a sanitarian, and a community worker all in one.

It must be emphasized that the Health Visitor program is not one of training "feldshers," or "half-baked" physicians, but rather a study of the use of subprofessional workers who are constantly under the direction of the public health nurse. Each Health Visitor has an assigned group of patients all residing in a particular area, and when out in the field, the Health Visitor regularly communicates with and receives instructions from either the nurse or the physician by radio-telephone installed in the automobile. At the present time a single public health nurse can manage the activities of three or four Health Visitors. The latter can perform all immunization procedures, can administer penicillin and other medication that must be injected, can obtain the patient's basic history, can assist in obtaining the history of the current complaint, and can perform many of the tasks that so frequently consume the time of more highly trained personnel. The types of relationships that are developing between the Navajo Health Visitors and the community on the one hand, and between Health Visitors and the professional staff on the other hand, are being studied in detail by the social scientists.

Segmental Studies

The term *segmental* is used to describe studies in areas that are more sharply defined than the three areas of the general investigations. The range of subject matter in the segmental studies is understandably broad. As a consequence, the research necessarily involves the use of both "field" techniques, in the epidemiologic, genetic, and social-anthropologic studies, and laboratory techniques, for such studies as those on viral disease, anemias, and coronary arterial disease. Segmental studies are in progress for each of the problem disease areas included in the community disease-pattern investigation, and such studies are also in progress in a number of other areas. No attempt will be made to present a complete listing of the studies, but four are briefly outlined to illustrate the varied techniques involved, the type of problem encountered, and the fact that the particular questions chosen could not really be profitably studied by either the medical or the anthropologic investigators working alone.

Self-Administration of Drugs

The first is a study of the extent to which an uneducated, nonliterate people (with partially educated children) can assume personal responsibility in a tuberculosis therapy or prophylaxis program based on the long-continued daily self-administration of isoniazid tablets. Although this question is being studied in terms of drug therapy in tuberculosis,

in reality the point at issue has far wider implications. For one of the major trends in medicine today is the unprecedented extent to which successful control of disease has come to depend on long-continued daily self-administration of a variety of powerful drugs by completely asymptomatic patients. To be faithful in the daily ingestion of a pill appears to be strangely difficult in any society. As the act is usually closely related to such personal habits as morning ablutions, the circumstances that surround it may be quite different in different cultures. The first step chosen in the study under discussion was simply to prescribe daily isoniazid tablets for an 18-month period for a group of 150 persons, two-thirds of whom were children. The degree of effectiveness of this practice was evaluated by the only means then available—namely, analysis of the patients' requests for additional supplies of the drug, supplemented by random visits for "pill inventory" in the hogans. By this admittedly crude method it was estimated that approximately 75 percent of the people managed their chemotherapy satisfactorily; an additional 10 percent did so if they were regularly prodded and supervised; and approximately 15 per cent of the group, for one reason or another, could not be relied upon to do their part. The obvious next step was to define these three crudely differentiated groups more precisely, so that the relevant individual factors might be identified. Before this could be done, however, it was first necessary to develop a laboratory technique, suitable for field conditions, whereby the fact that the drug had been recently ingested could be established. Several procedures for chemical analysis of the urine were available but were not satisfactory for conditions as they existed in the field (*2*). For it was essential that the procedure should not involve the administration of any new chemical compound of undefined toxicity; the discoloration of the urine or a marked change in its odor; or any chemical extraction process or technique of similar complexity, beyond the capacity of the subprofessional Navajo laboratory workers to carry out. In association with Gladys Hobby, a technique was developed that met these criteria (*3*). The vitamin riboflavin is incorporated in the isoniazid tablet, and the presence of the riboflavin in the urine is easily detected by its capacity to fluoresce. It has thus become technologically possible to return to the field studies, but because of certain social problems it is essential to proceed with caution. For in order for the technique to be useful, it will be necessary at some time to reveal the information it discloses. Once this is done, there will occur a change in the relationship of family and physician from one of trust to one of resentment of a mysterious form of "inspection." This problem in itself can presumably be managed through careful conduct, but there is a further problem that is even more delicate. This has to do with the fact that certain Navajo are members of a cult that use the alkaloid peyote in a religious ceremony. This practice has been outlawed by the Tribal Council, and if the practice of peyotism can be proved, the user is subject to a sentence in jail. In the course of the tuberculosis studies at Manyfarms, but before the particular riboflavin technique had been developed, it was discovered that families from certain camps were reluctant to participate.

An entire family leaving their camp for a trip to the field clinic for examination, because the father was recently discovered to have pulmonary tuberculosis in a potentially infectious stage. In the left foreground is a "shade" or temporary summer dwelling. The permanent hogan may be seen in the background. Approximately half of the transportation in the area is by horse; the remainder is by automobile, chiefly by "pickup" truck. The family was found to be free of infection, and the father is receiving self-administered antituberculosis chemotherapy, with periodic supervision by a Health Visitor and the professional staff. [Kenneth Marthy, Chappaqua, N.Y.]

On discrete inquiry it developed that they had heard a rumor that a test was available for the identification of peyotists by detection of the material in the urine. By treading a difficult course between the obvious wishes of the Tribal Council to stamp out peyotism on the one hand and the desire to obtain patient cooperation on the other, it was possible to "get the word around" that no such test was known to the staff. This process now has to be repeated, and whether this can be done successfully remains to be seen.

Thus it is that a "drug self-administration" study that has proceeded "logically" from the investigator's standpoint has developed its own set of complications. The experience represents one more example of a principle familiar in cross-cultural work in any field—namely, that a technique which produces information is looked upon as something quite mysterious, and hence may be accorded a completely unpredictable role in terms of the prevailing fears of the culture.

Translation of Medical Concepts

The second of the segmental studies that deserves mention is that on the subject of "conceptual transfer." This study is being conducted by both the social and the medical scientists in association with a noted student of the Navajo language, Robert Young. The basic techniques involve the paraphrasing of passages from a selected medical textbook into two English versions—a version readily intelligible to a person of average education in the United States, and a version thought to fit Navajo concepts. The two versions are then translated orally into Navajo by a number of persons who bear a greater or lesser responsibility as interpreters at medical facilities in the Navajo country. The translations are recorded and are analyzed as they are retranslated into English. The disease descriptions include diseases familiar to the Navajo and diseases concerning which they have no knowledge.

Certain of the points established thus far are general ones that are presumably valid in fields other than health. For example, it was discovered that the common practice of defining with synonyms gave rise to considerable difficulty. Some interpreters presented with the statement "the disease known as arthritis or rheumatism" would proceed to attempt to describe two separate diseases from that point on. A more important specific finding, however, has been that the problem of physician-patient communication with Navajo people is a formidable one, not so much because there are wide differences between the Navajo and the English language as because there are wide differences between the two cultures with respect to concepts of bodily disease. If both cultures had essentially the same concepts of disease and its treatment, any person reasonably fluent in both languages could serve as a satisfactory "bridge" between the patient and his physician. As it stands, however, with the wide difference in medical concepts that exist, an interpreter may be completely bilingual in discussing the ordinary affairs of life yet wholly unreliable in discussing medical matters unless he is quite generally familiar with the medical concepts of both cultures.

To be sure, this same principle applies in some degree to technologies other than medicine. But in most other technologies—for example, animal husbandry or agriculture—the two people involved in the attempt at communication are both usually concerned with the visible world around them and not with the inner feelings of one of the two persons. By contrast, for the proper application of modern medicine the physician depends to a very considerable extent (exclusively, for some diseases) on the subtleties and minor gradations in the patient's own account of how he feels as compared with his usual state.

Thus, in the case of the Navajo, the patient's own standards, by which he judges his degree of well-being, are not only not known to the physician but they derive from concepts of whose very existence the physician may be unaware. It is possible to learn about the concepts from the person serving as interpreter, but this is a lengthy process and the sessions must be conducted in private. For to establish effective interchange with the patient it is essential that the interpreter should not be placed in a position of embarrassment with one of his own people because of a particular approach used in questioning. Ideally, the physician should learn both the concepts of health and the language of the community in which he is working. But for him to acquire the language, particularly to a degree that would permit him to make fine distinctions among symptoms, is frequently not practicable.

An approach that is practicable is to train the physician and the technicians to work effectively through interpreters. The principal lesson already learned, however, is that for effective interchange it is necessary for both the physician and the interpreter to acquire a very considerable body of information concerning the disease concepts in the two cultures. And the educational effort necessary to train the interpreter in "Western" medical concepts is very little less than that necessary to train him as an effective subprofessional technician. Consequently, at least in the specific case of cross-cultural work in medicine and health, there is no real place for a special training-school for interpreters. It is more realistic to go the whole way and train the subprofessional auxiliaries of the physicians and nurses.

Ischemic Heart Disease

The third study for mention is one concerned with ischemic heart disease—that is, the myocardial damage that results from coronary arterial disease. Impressive evidence has been accumulated in recent years that this disease is culture-linked. The factor in various cultures that is most often singled out as perhaps the most significant in this disease is the amount of fat, specifically the amount of hydrogenated fat, in the diet. It has been thought that the Navajo, like many peoples who live in relatively primitive surroundings, have a low prevalence of ischemic heart disease, but that, unlike most such peoples, the Navajo consume a diet high in animal fat. It seemed of importance, therefore, to test the long-held clinical impressions that ischemic heart disease was rare among the Navajo by making detailed clinical, electrocardiographic, and other laboratory studies on all members of the Manyfarms-Rough Rock population who were 30 years of age or older. If the suspected low prevalence were to be confirmed, the impression that the people consume relatively large quantities of animal fat could then be tested, and indeed any other culturally-linked factors that might reasonably be thought to have significance could be studied.

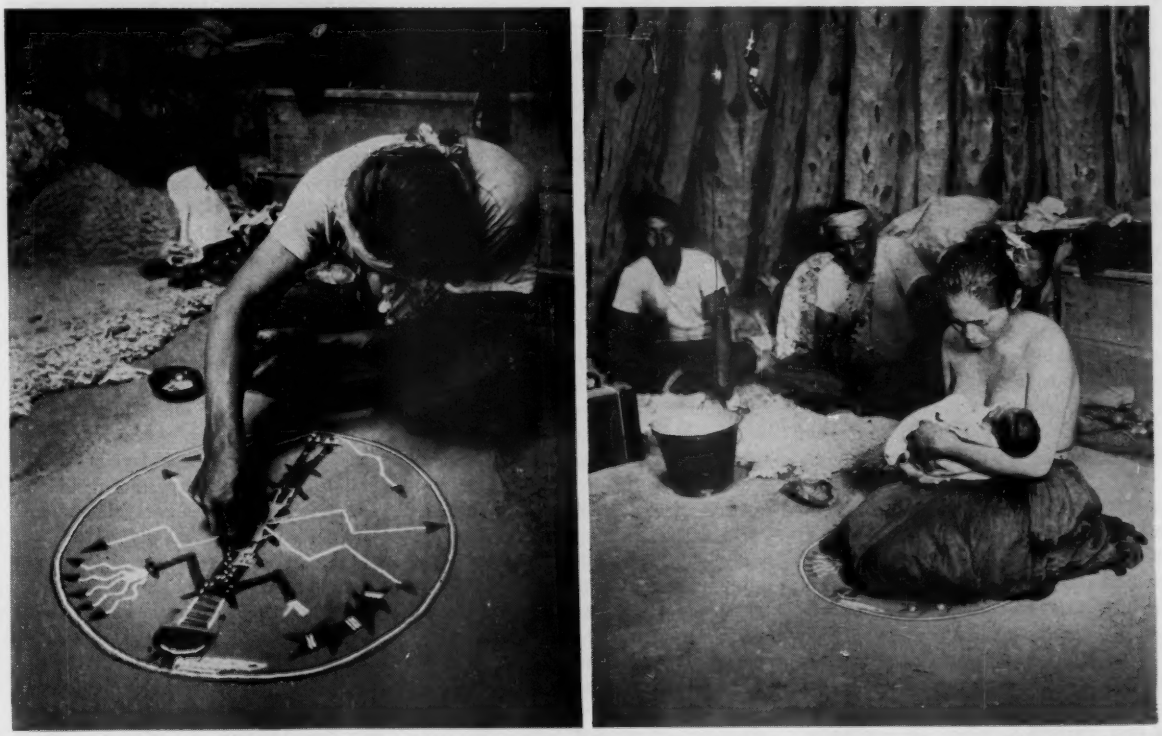
The suspicion that the prevalence of ischemic heart disease was low was definitely confirmed, and the other studies were started. The observations made thus far have included complete histories and physical examinations on approximately 500 of the 600 persons 30 years of age or older; electrocardiograms with standard and unipolar leads;

measurement of the serum cholesterol; determinations (in selected groups) of the pattern of urinary excretion of 17-ketosteroids and ketogenic steroids (*4*); characterization of the daily diet by investigators who arranged either to live with a number of the families or who made systematic visits to a larger sample at mealtime; determination (by the same observers) of sleeping habits; measurements of cigarette consumption; and crude estimates, based merely on observation, of the amount of physical exercise generally involved in hogan living. In addition, studies of the fatty-acid composition of samples of fat obtained by biopsy of appropriately selected subjects are in progress; actual measurement of physical exercise has been made; and an attempt is being made to measure crudely what might be termed "relative peace of mind" by ascertaining the number and the effectiveness of religious ceremonials held for this purpose among an appropriately selected population sample. (Navajo religious ceremonies are not held on a regularly scheduled basis but are organized on an *ad hoc* basis, according to the particular needs of an individual.)

As indicated above, virtually all of these data have been obtained, except in the last three areas, and the data are now undergoing analysis. Consequently, only very tentative statements can be made at this time. When due allowance has been made for this fact, however, it appears that the prevalence of ischemic heart disease is indeed low [three cases in a three-year period among the approximately 600 (actually 607) people 30 years or older]; that the apparent absence of angina pectoris is not a reflection of failure of "conceptual transfer" on the part of the interpreters; that the range of values for serum cholesterol is the same as for urban dwellers in the United States; and that consumption of cigarettes is rare and, when found, is low (maximal consumption being 40 cigarettes weekly). It further appears (although the analyses are less complete) that the usual diet will be found to approach the United States average in terms of content of fat; that the obvious differences between Navajo and non-Navajo in terms of hair distribution are not accompanied by significant changes in the pattern of hormone excretion in the urine; and that aortic calcification occurs at a later age in the 50- to 69-year age group among Navajo than among non-Navajo. It is believed, therefore, but it cannot as yet be stated as definite, that of the factors studied, the principal differences between the Manyfarms-Rough Rock Navajo and residents of urban communities in the United States may be found in such factors as amount of physical exercise, duration of sleep, consumption of cigarettes, and perhaps relative "peace of mind."

Medicine Man and Physician

The fourth segmental study to be mentioned has to do with relationships between the Navajo medicine man and the "Western" physician, and the effects of these relationships on community life. This study has two components. The first is an investigation of what might be termed "the healing process" in a selected sample of nine families. An attempt is being made to determine what is considered to be a health problem in the home and what factors appear to determine whether help is first



(Left) A medicine man makes a "sand painting" on the earthen floor of a hogan, with earth pigments, in preparation for a healing ceremony. [Courtesy of the American Museum of Natural History] (Right) A Navajo mother with a sick child kneels on the sand painting during the healing ritual. The medicine man may be seen in the background. [Courtesy of the American Museum of Natural History]

sought from the Navajo medicine man or from the physician. The other component of the study has to do with the reactions of the medicine men themselves and with whether, as a consequence of the availability of "Western" medicine, young men are no longer willing to expend the not inconsiderable effort necessary to acquire status as medicine men. Thus far the relationships between the medicine men in the community and members of the project staff have been excellent. Every effort is made to accord the medicine men the respect they deserve as the spiritual leaders of the community. Many of the medicine men themselves consult the physicians as patients, and they have raised no objections to the use of "Western" medical methods for patients they are caring for by Navajo methods. Nevertheless, an obvious potential problem exists in any attempt to preserve the spiritual influence of the medicine man while removing from him responsibility for the management of "somatic" disease. The medicine men believe they can distinguish between the type of "illness" most likely to be benefited by their procedures and the type that is better managed by the project staff. Moreover, they are quick to recommend the employment of both sets of "healers" in situations that appear to have any urgency. The danger obviously exists, however, that an acute illness that could be easily treated by modern medical methods might be allowed to progress significantly while Navajo medicine men were being employed. Thus far this has happened only rarely. It is to be hoped that the issue may not become serious and that the present good relations can lead both parties to make adaptations in their practice that will make it possible to preserve the essentials of both "ways."

Significance of the Study

It seems appropriate to comment on the problems involved in the evaluation of studies such as those under discussion and on the possible applicability of any findings to cross-cultural medical technologic development in general.

One of the obvious problems that has to be faced in mixing medical and social-science studies in a single whole is that methods suitable for evaluation in one field cannot always be adapted to another. In the Manyfarms project, the drawing of inferences from the data consists of evaluating a variety of observations, of widely different nature, on the influence of the technology on the community. Some of these observations can be expressed numerically, but many cannot. Thus we have to find ways of arriving at conclusions based on a mixture of various types of evidence.

It would be foolish to defer facing the fact that in many of the issues of greatest importance, the major inferences, in the last analysis, are in the form of subjective judgments. Every effort has been made, therefore, to ensure that the observations and the subjective judgments are made in as systematic and organized a way as possible, and that the conclusions represent the consensus of the greatest number of people in a position to make an informed judgment. It appears that the strictly medical findings should have generality. What cannot be decided at present, however, is whether the particular observations that have to do with working with a people represent research findings that have generality, or whether they merely represent experience, and a certain wisdom presumably acquired thereby, that must remain an essentially individual affair.

Many problems remain that are not being studied. Certain of these are beyond the scope of the project or the competence of the present investigators; others represent wholly proper research subjects for which no approach has as yet been imagined. Nevertheless, they deserve brief mention.

There is the fascinating question of the character of the period during which a community might have the "best of both worlds," when its "primitive" pattern of disease has been suddenly suppressed artificially, rather than by the century and a half of socioeconomic development that produced the same result in our society. Is it not possible that we achieved this result at too high a price, as reflected by the particular diseases that are plaguing us today? Will the artificially altered communities necessarily follow directly in our footsteps, as seems to be tacitly assumed. Might it not be that a people who will necessarily continue to live for some time in a rustic environment will develop wholly new disease patterns, quite unlike our own, as they adapt to this relatively isolated but drastic change in their environment. This whole subject is obviously no mere philosophic speculation, for even the preliminary data on births and deaths at Manyfarms strongly suggest the emergence there of just such a phase as "the best of both worlds."

Another major area has to do with the markedly changed sovereignty relationships of recent years, whereby technologic development activities are now almost invariably conducted with recipient governments and peoples who are politically independent of the nations supplying the bulk of the technicians. Even a nation's own trained people are frequently quite alien to its rural peoples and exert only nominal political authority over them. This general phenomenon has many implications, but a major one is that to all intents and purposes public health programs today are obliged to proceed solely by persuasion. But "persuasion" in a cross-cultural situation is a highly deceptive word, for it really means the use of an enormous body of information and skills that have nothing to do with technological knowledge. Moreover, in most economically underdeveloped areas, persuasion in the area of health must proceed without the powerful support of an immediate prospect of rapid change in social and economic status. Such a hope for improvement of social status has undoubtedly been a very powerful force in determining our own hygienic practices as individuals.

It must also be noted, as was recently emphasized by the Banfields (*5*), that the degree of community organization necessary for the exploitation of a technology does not necessarily arise automatically just because the technology is made easily available, and that in some cultures the necessary organization may not arise at all. With the Navajo, the problem of organization should not prove too difficult because the tribal organization is rapidly assuming a well-directed responsibility for the management of its affairs. Inevitably there will be some lag between effective organization at the general tribal level and effective participation by the individual communities in their own affairs. The latter is something that differs widely in degree at present among the many "communities" of the large tribal area.

How Rapid the Change?

It would not seem proper to close this consideration of certain aspects of research in technologic development without mention of the pace or rate of the introduction of a technology. Cer-

tainly it is not clear whether this is something that is controllable or even susceptible to study or whether, once a significant innovation is made, others inevitably follow in an essentially uncontrollable fashion. In large measure, any attempt to control the pace of introduction of a technology involves ethical considerations, and these become of primary importance when the technology is medical. With the Manyfarms project we have not really had to face up to this formidable question. For many delays, of a type to be expected in any field program, resulted in a situation in which we could not have simultaneously introduced the many individual elements of a total program even if we had wanted to do so. Consequently, we have tended to introduce one thing at a time. Moreover, in making our choices we derived considerable freedom from the fact that the governmental and tribal programs are both expanding at such a rate that by the time our long-term studies are completed, any appropriate services from our program can be maintained.

In most development programs in health, however, this question of pace looms importantly, especially in the case of programs devoted to the control of a single disease, such as tuberculosis. Unless we can acquire wisdom in this matter, the possibility of actually doing harm through technologic development programs in health is very real. At the present time, however, we cannot pretend that we have found a way to investigate this question of "rate of introduction" in the Manyfarms studies and can only state that we are devoting considerable attention to attempts to find such a way. In the meantime, in our thinking we try to be guided by the thought expressed several years ago by the distinguished former United States diplomat George Kennan (*6*): "Wherever the authority of the past is too suddenly and too drastically undermined—wherever the past ceases to be the great and reliable reference book of human problems—wherever, above all, the experience of the father becomes irrelevant to the trials and searchings of the son—there the foundations of man's inner health and stability begin to crumble. Insecurity and panic begin to take over, conduct becomes erratic and aggressive. These, unfortunately, are the marks of an era of rapid technological or social change. A great portion of our globe is today thus affected. And if the price of adjustment to rapid population growth is to cut man's ties to the past and to catapult him violently across centuries of adjustment into some new and unfamiliar technological stratosphere, then I am not sure that the achievement is worth the price."

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Science in the News

Scientific Activity in Africa Growing; U.S. Education Aid Rising Slowly

The political and economic changes that are taking place in many African countries as they struggle for independence seem to be stimulating rather than retarding scientific activity.

Munitalp Meteorological Institute

A recent event that augurs well for African science is the announcement that an Institute of Tropical Meteorology is to be established in Kenya with funds provided by the Munitalp Foundation. This news was reported on 1 December by Lord Twining, chairman of the board of the foundation, when he welcomed scientists from 26 countries to the opening of a 17-day symposium on tropical meteorology that took place in Nairobi, capital of Kenya. Kenya is a British colony and protectorate that is seeking independence. The symposium was sponsored by Munitalp and the World Meteorological Organization.

The Munitalp Foundation will contribute £40,000 for capital expenditure on buildings and equipment and £12,000 a year for 10 years to meet operating costs. The institute will probably be located in Maguga, on the outskirts of Nairobi.

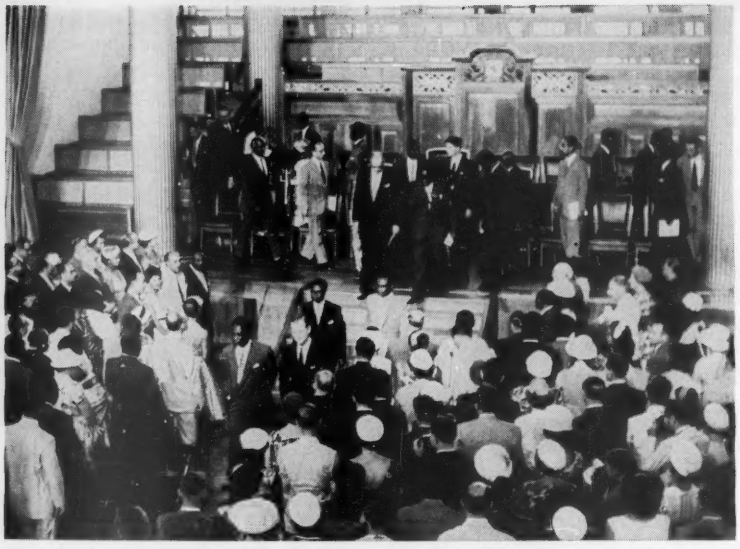
Munitalp ("platinum" spelled backwards), which has now transferred its headquarters to Africa, was incorporated in 1949 in the state of Connecticut. The foundation has long supported basic meteorological research in the United States—research such as the cloud physics investigations of Vincent Schaefer.

In his December announcement, Lord Twining explained that agreement had been reached with the East African High Commission for the new institute to be associated with the East African Meteorological Department and with the East African Agricultural and Forestry Research Organization in Maguga. He emphasized that while the institute would work in close cooperation with these two bodies, it would retain its independence and would be free to carry out work for the benefit of all countries in tropical Africa.

Lord Twining invited the countries and organizations participating in the Nairobi symposium to cooperate with the new organization, pointing out that although the institute will initiate and conduct particular investigations, among its most important functions will be the collection and collation of data and the dissemination of knowledge.

United States Delegate Comments

V. D. Rockney of the U.S. Weather Bureau in Washington, who attended



Prime Minister Nkrumah and Prince Philip, Duke of Edinburgh (center), leave a hall in Accra after inauguration of the Ghana Academy of Science and Learning.

the Nairobi symposium, strongly recommends that the United States detail one or two "really top" meteorologists to work at the new institute. He points out that if a number of countries lend experienced investigators, the institute will quickly be provided with a superior research corps that can make a real contribution to the progress of African science. He stressed the supranational character of the project, pointing out that the organization hopes to attract research workers and students and to secure contracts from many countries in Africa.

Rockney also mentioned that he was impressed by the extent of African participation in the Nairobi symposium. Some 17 states and territories were represented. Each delegation was composed of the chiefs of the state meteorological services, and in most cases at least one of these was a native African. In addition, Rockney made special reference to an unusually effective banquet address of thanks that was delivered on behalf of all the visitors by I. O. Emore of the Meteorological Service of Nigeria.

Ghana Academy Established

Another development that demonstrates a rising interest in science in Africa is the recent establishment of the Ghana Academy of Science and Learning. On 27 November Prince Philip, Duke of Edinburgh, visited Accra to officially open the new academy, which was organized at the initiative of Prime Minister Kwame Nkrumah. Ghana is a newly independent member of the British Commonwealth and will change its form of government from a monarchy to a republic on 1 July.

The objectives of the academy are to promote study and dissemination of knowledge in all fields of science and learning, to establish and maintain standards of endeavor in these fields in Ghana, and to recognize outstanding contributions to the advancement of science and learning in Ghana. The new organization has 20 members. The Duke of Edinburgh has agreed to serve as president for the first 2 years; Prime Minister Nkrumah is chairman.

First Federal Congress Scheduled

Still another evidence of increased scientific activity in Africa is the organization of the First Federal Science Congress, a meeting of international scope that is to be held at the University College of Rhodesia and Nyasaland, Salisbury, Southern Rhodesia, 17–21 May. Salisbury is the capital of the Federation of Rhodesia and Nyasaland, which consists of Northern Rhodesia and Nyasaland, protectorates, and Southern Rhodesia, a self-governing colony. This is the first congress of its kind to be held within the boundaries of the federation; it is being supported by the scientific societies and associations in the federation, as well as by the larger industrial and mining organizations.

The theme of the congress is "Science in Central Africa." There will be three sections, one in the physical sciences, including geology, meteorology, and engineering; one in the biological sciences, including medicine and agriculture; and one in the social sciences, including pre-history and archeology.

More detailed information may be obtained from the secretary general of the congress, Dr. D. F. Mettrick, University College of Rhodesia and Nyasaland, Private Bag 167H, Salisbury, Southern Rhodesia.

United States Aid Increasing

The United States is just beginning to make substantial contributions to the training of African scientists. A Weather Bureau spokesman says that of the 182 people who have come to this country during the last 10 years to be trained in meteorology under government auspices, only seven were from Africa, although meteorology, because of its bearing on agriculture, is one of Africa's most important sciences. He indicated that this proportion was probably typical for other fields of science.

Figures released by the Institute of International Education on public and private United States support of foreign scholars show that although the number of visiting African faculty members in all fields rose between 1957 and 1959, the rise was only from 24 to 42. The majority of these faculty members were scientists, as indicated by the following breakdowns (the first figure is for 1957, the second for 1959): agriculture—0, 2; business administration—2, 3; education—1, 2; engineering—1, 7; humanities—5, 6; medicine—4, 6; natural and physical sciences—4, 11; social sciences—7, 5.

African students in this country in 1957 totaled 1424; 170 of these were in the medical sciences, 213 in the physical and natural sciences, and 48 in sociology, psychology, and social work. In 1959 the over-all figure rose to 1735; there were 165 in the medical sciences, 252 in the physical and natural sciences, and 65 in sociology, psychology, and social work.

Although they show some increases, the numbers are small, especially when the figures are compared, for example, with those for the Near and Middle

East, a somewhat similar area. In 1957 there were 65 faculty members from the Near and Middle East in this country and 5243 students; the 1959 totals are 132 faculty members and 6619 students.

House Committee to Provide Forum for Scientists

A group of scientists has been invited to use a congressional committee as a forum in which they can present their ideas. Chairman Overton Brooks (D-La.) of the House Committee on Science and Astronautics reports that 12 scientists and engineers have agreed to serve on a science advisory panel to aid the committee in its work. The members of the panel will meet with the committee once or twice a year.

The Science and Astronautics Committee, which is entering its second year of operation, is the first committee in Congress to be devoted to science in general. In announcing the new advisory group, Brooks said:

"It is unfortunately true that too many times scientists with important ideas that would help advance the interests of the United States and mankind in general have been unable to find anyone to listen to them. Theirs have been, on too many occasions, voices in the wilderness.

"Now, through this panel, we shall make available to them a public forum in which they can be heard. If their proposals have merit, and I am confident they will, the Committee will give them the utmost consideration and, if necessary, enact such legislation as is required to carry them out."

Panel Members Named

The members of the advisory panel, the fields in which they specialize, and their affiliations are as follows: Edward J. Baldes, biophysics, senior consultant, Mayo Clinic; Clifford C. Furnas, chemical engineering, chancellor of the University of Buffalo; Martin Goland, applied mechanics, Southwest Research Institute, San Antonio, Tex.; W. Albert Noyes, Jr., general chemistry, University of Rochester; Clarence P. Oliver, genetics and zoology, University of Texas; Sverre Petterssen, meteorology, University of Chicago; Roger Revelle, geophysics and oceanography, director, Scripps Institution of Oceanography, University of California, La Jolla; Richard L. Russell, geology, Louisiana State University; H. Guyford Stever, aeronautical engineering, Massachusetts Institute of Technology; James A. Van Allen, nuclear physics and cosmic rays, State University of Iowa; Fred L. Whipple, astronomy, director, Astrophysical Observatory, Smithsonian Institution, Cambridge, Mass.; and Maurice J. Zucrow, jet propulsion, Purdue University.

Canada's Oceanographic Research To Be under New Committee

The Canadian Government has set up a committee to coordinate and direct its work in oceanography and to represent the government internationally in the field of oceanographic research. In a move to insure that Canadian research in oceanography is carried out on an integrated basis and, at the same time, to maintain the necessary international liaison with other countries doing similar research, the Canadian Government has reorganized its Joint Committee on Oceanography and renamed it the Canadian Committee on Oceanography.

Federal agencies interested in oceanography are the Royal Canadian Navy, the Fisheries Research Board, the Department of Mines and Technical Surveys, the Defence Research Board, the National Research Council, and the Meteorological Branch and the Marine Services of the Department of Transport. The new committee will comprise representatives from these agencies as well as from universities interested in this field of work. W. E. van Steenburgh, director general of scientific services of the Department of Mines and Technical Surveys, has been selected chairman of the new committee, and H. B. Hachey of the Fisheries Research Board has been named secretary.

Growing awareness throughout the world of the vital current importance of oceanographic research has focused attention on the necessity for such research in countries like Canada, which possess long coast lines and extensive continental shelves. More recently, Canada's need for a national committee empowered to represent the government on international committees has been evident. In particular, the new committee will represent Canada at the Special Conference on Oceanographic Research (SCOR) of the International Council of Scientific Unions and on the NATO Scientific Committee on Oceanographic Research.

The reorganization of the Canadian Committee on Oceanography, by providing better coordination of federal activities in this field with the work of the universities, will give added impetus to Canada's program in oceanography. A major feature of this program is the establishment on the east coast, under the Department of Mines and Technical Surveys, of a $3-million oceanographic institute, to be known as the Bedford Institute of Oceanography. The new institute, which will have facilities for study in any phase of the science, is being built in Bedford Basin near Halifax. Construction will take 5 years. When the institute is in operation it will have a staff of some 300 oceanographers, hydrographers, submarine geologists, geophysicists, and other scientific personnel, plus supporting staff, and an operating fleet of ten oceanographic and hydrographic vessels.

William M. Cameron, leading Canadian authority on oceanography and director of plans of the Defence Research Board, will direct the expanding oceanographic research program of the Department of Mines and Technical Surveys. He will have charge of the over-all development of the new Bedford Institute.

The Fisheries Research Board and the Department of Mines and Technical Surveys will completely coordinate their oceanographic activities on the east coast; the physical oceanographers of the Fisheries Research Board will be housed in the institute, while the board's biological research activities will continue to be located at St. Andrews, New Brunswick.

A multi-million-dollar shipbuilding program will provide the fleet of vessels. The first of these, the $7-million *C.G.S. Hudson*, is expected to be commissioned in 1961.

On the west coast, Canadian oceanographic investigations are carried out by the Pacific Oceanographic Group of the Fisheries Research Board; this group will maintain close liaison with the committee.

In the Arctic, Canada has already initiated a broad program of research along the hundreds of miles of continental shelf that comprise the rim of the Arctic Basin. One phase of the study deals with the oceanography of

the Arctic Ocean and the main channels between the islands. The project, known as the Polar Continental Shelf Project, is also being handled by the Department of Mines and Technical Surveys.

The original Joint Committee on Oceanography came into formal existence in April 1946, to continue the cooperative work on the oceans carried on between agencies of the federal government during World War II. Reorganization of the committee as the Canadian Committee on Oceanography, with national status, is indicative of the marked broadening of Canadian interest in oceanography both at home and abroad.

Academy Report Stresses Need for Scientific Experimentation in Quest of Weather Control

If we are ever to succeed in our efforts at weather modification we must first change our methods of experimentation, states a report issued recently by the National Academy of Sciences–National Research Council. The report observes that many scientists regard the atmosphere as a natural resource of great magnitude. But, the report continues, present efforts to gain the basic knowledge needed to exploit this resource are small compared to the benefits to be gained from such use.

In stressing the need for fundamental understanding of atmospheric processes, the report distinguishes between experiments designed to produce basic data and experiments designed to produce rainfall. Acknowledging that cloud-seeding efforts during the past decade have contributed to our knowledge of weather phenomena, the report notes that they have also led to many "false starts" and that "the economic value of obtaining even a small degree of control over rainfall has created undesirable pressures which have tended to dilute the scientific quality of some weather-modification experiments."

The meeting on which the report is based was "The Skyline Conference on the Design and Conduct of Experiments in Weather Modification," organized by the Academy–Research Council's Division of Mathematics, which is under the chairmanship of Samuel S. Wilks, professor of mathematics, Princeton University. Thirty-one meteorologists and statisticians from the United States, Canada, and Australia attended the conference 1–3 May 1959, at Big Meadows Lodge, Shenandoah National Park, Va. The conference was initially suggested by Earl G. Droessler, director of the National Science Foundation's Atmospheric Sciences Program, which provided financial support.

The conferees found strong scientific reasons, apart from considerations of immediate economic gain, for concentrating initial research along the lines of precipitation control. These reasons include the possibility that in such research might be found the key to an understanding of energy balance in weather systems. Such a key would provide man with the ability to control not only rain and snow but also hail, lightning, and violent storms.

Other Problems

In addition to its comments on cloud-seeding and the inclusion of a compendium of the best known and most important weather-modification experiments undertaken in the last decade, the report makes the following points.

1) Laboratory and field studies should be carried out by individual researchers or small groups of scientists. Although such projects will be largely of an exploratory nature, the results, if promising, can be subjected to large-scale experimentation and statistical analysis. There is need for experiments to determine, for example, the relation between lightning and cloud-top temperature or to determine easily measured cloud parameters in various types of clouds, need for cloud-modification programs involving small geographical areas or individual clouds.

2) Statisticians must be enlisted to work with meteorologists as collaborative weathermen. In his foreword to the report, Wilks says: "The degree of success so far achieved by various research programs in weather modification is, in large measure, due to detailed and skilled analysis of the data which combines sound statistical technique and enlightened meteorological insight."

3) Where effective cooperation exists between meteorologists and statisticians, in universities and research institutions, it should be strengthened. Where only one group exists or is effective, the other should be created or bolstered. Fellowship programs should be established to encourage young scientists to enter these areas. Summer study groups, summer institutes, conferences, and seminars are needed for meteorologists, statisticians, and other scientists interested in weather modification.

4) Very few experiments thus far conducted in the United States have been carried out over a long enough time span. None, for example, can match the Australian Snowy Mountain project that began in 1955 and is still continuing. Most field experiments must be operated for several years if they are to yield enough information to be conclusive. At the same time, they should be conducted to yield information on a number of questions.

5) Experiments must be repeated in space as well as in time. Related to this requirement is the need for improved measurements, improved instrumentation, and standardized terminology. Meteorological categories such as "storm," "cloud suitable for seeding," and "day suitable for seeding," for example, must be objectively defined.

6) Basic research programs in atmospheric physics, chemistry, and electricity should be considerably augmented. Laboratory studies should extend into such areas as solid-state physics, crystallography, surface chemistry, and electron microscopy. Basic studies should also be conducted on specific weather systems, such as shower clouds, clouds influenced by mountains, hailstorms, lightning storms, and cyclonic systems.

Grants, Fellowships, and Awards

Anthropology. Two resident research fellowships, to be known as the Ogden Mills fellowships, are to be awarded annually by the department of anthropology of the American Museum of Natural History, New York City. The fellowships are intended for anthropologists who might benefit from a year at the museum, through having access to the anthropological collections, the library, and other facilities of the museum and through working in conjunction with members of the curatorial staff. There is no specific limitation on the kind of anthropological research that may be done under these fellowships, but preference will be given to those applicants who can make use of the museum's collections and archives (unpublished field notes, films, sound recordings, and so forth) either in the elaboration of special studies or in connection with research that they, or members of the curatorial staff, may

have under way. These fellowships are not intended for the support of field work, but it is possible that such activities may occasionally be included.

Candidates who have recently received their doctoral degrees will be given preference, but there are no rigid requirements in terms of age, sex, degrees, or academic background. Selections will be made by the staff of the department of anthropology, and the right is reserved to withhold the award of fellowships in any given year.

The period of the fellowships is for 1 year, beginning 15 June; the stipend is $5000. The first awards will be made for the year 1960–61.

Applications should include a full curriculum vitae, a letter describing the candidate's research aims, and supporting references. Applications should be submitted *before 1 March* to Dr. Harry L. Shapiro, Department of Anthropology, American Museum of Natural History, New York 24, N.Y.

Chemistry. The Division of History of Chemistry of the American Chemical Society is now asking for nominees to be considered for the 1960 Dexter Award in the history of chemistry, which is administered by the division. The award is made on the basis of services which have advanced the history of chemistry, such as the following: publication of an important book or article; furtherance of the teaching of the history of chemistry; significant contributions to the bibliography of the history of chemistry; or meritorious services over a long period of time which have resulted in the advancement of the history of chemistry.

All information, in duplicate, should be sent *by 10 March* to the secretary of the Division of History of Chemistry, Sidney M. Edelstein, Dexter Chemical Corporation, 845 Edgewater Rd., Bronx 59, N.Y.

Nephrology. A grant to provide travel funds for participants in the First International Congress of Nephrology, to be held in Geneva, Switzerland, 1–3 September, has been awarded by the U.S. Public Health Service to the American Society for Clinical Investigation. Members and nonmembers are eligible to apply for the funds, which are sufficient to send 20 people to the meetings. Applications should include, in quadruplicate, a curriculum vitae and a letter of application stating the basis for the applicant's interest in the field and in the congress. Applications should be sent before *1 March* to Saul J. Farber, Secretary, American Society for Clinical Investigation, New York University College of Medicine, 550 First Ave., New York 16, N.Y.

Nutrition. The National Vitamin Foundation wishes to bring to the attention of those engaged in clinical and basic research in the field of nutrition, biochemistry, and metabolism its current interest in the support of research, preferably on man, most likely to advance understanding of the diverse metabolic functions of the vitamins. The foundation wishes to encourage research on vitamin nutrition and metabolism in the areas of (i) mental health and (ii) side-reactions to drugs, and it invites applications for grants in support of such research.

Announcement of the new research interests of the foundation should not be interpreted as eliminating consideration of applications for grants-in-aid of research on other aspects of vitamin metabolism and nutrition. Application forms may be obtained from the offices of the foundation at 149 E. 78 St., New York 21, N.Y. The foundation takes action on applications twice each year, in the spring and fall. For grants to be effective on 1 July, applications should be mailed before *1 March;* for January grants, applications should reach the foundation by *1 September.*

News Briefs

Earthquake engineering. The second World Conference on Earthquake Engineering will take place 11–18 July 1960 in Tokyo and in Kyoto, Japan. The Science Council of Japan, a governmental organization, is organizing the conference with the cooperation of the Japan Society of Civil Engineers, the Architectural Institute of Japan, and the Seismological Society of Japan. For information, write to Professor Kiyoshi Muto, Chairman, Organizing Committee, Second World Conference on Earthquake Engineering, Science Council of Japan, Ueno Park, Taitoku, Tokyo, Japan.

* * *

Chemical index. *Index Chemicus,* a monthly index to 50,000 new chemicals reported each year in the scientific literature, will be published by Eugene Garfield Associates, 1122 Spring St., Philadelphia. The first issue will appear early in 1960. New compounds will be reported in the index within 30 days after original publication in the scientific literature.

* * *

Vulcanology program. A program in vulcanology, geochemistry, and petrology is being organized for the Helsinki meeting of the International Union of Geodesy and Geophysics, to be held 25 July–6 August. Symposia on geochronology, high-pressure chemistry, isotope geology, and atmospheric chemistry, as well as a general program in geochemistry and petrology, will be included. For information write to Irving Friedman (U.S. Geological Survey, Washington 25), secretary of the Section of Vulcanology, Geochemistry, and Petrology, American Geophysical Union.

* * *

Overseas library. The U.S. Information Agency has assembled a small library containing 30 of the best available American paperbacks in the fields of science and technology as a simple and inexpensive means of providing overseas readers with information. The agency has ordered 500 of these "package" bookshelves, which will be available on loan to educational institutions, science clubs, and other groups.

* * *

Biology news. The American Institute of Biological Sciences has announced establishment of the Biology News Bureau as a new activity to serve biologists and professional organizations in the biological sciences. The new AIBS unit has the assignment of smoothing the flow of information between the biological professions and the public.

Harold F. Osborne has been named director of the bureau. Osborne formerly was a science writer for the Seattle *Times,* an editor and correspondent for the Associated Press, and a member of the information staff of the Veterans Administration. The Biology News Bureau has offices at AIBS headquarters, 2000 P St., NW, Washington 6, D.C.

* * *

Nutrition certification. The American Board of Nutrition will hold the next examinations for certification as a specialist in human nutrition during the week of 11–15 April in Chicago, Ill. Application forms, which must be submitted before 1 March, may be obtained from the secretary, Robert E. Shank, Department of Preventive Medicine, Washington University School of Medicine, Euclid and Kingshighway, St. Louis, Mo.

Scientists in the News

The three Monograph Prizes, inaugurated last year by the American Academy of Arts and Sciences, have been announced for 1959. The awards, of $1000 each, were presented for unpublished monographs.

Walter H. Munk and **Gordon J. MacDonald** of the University of California won the physical and biological sciences prize for their geophysical discussion of the rotation of the earth.

Lawrence E. Fouraker and **Sidney Siegel** of Pennsylvania State University received the social science award for a manuscript on bargaining and group decision making.

William P. Malm of Los Angeles won the humanities prize for his exposition of Japanese Nagauta music.

Barbara Fish has been appointed associate professor of clinical psychiatry at New York University College of Medicine and psychiatrist-in-charge of the Children's Service of Bellevue Hospital Center. Formerly she was assistant professor of clinical pediatrics and instructor in psychiatry at Cornell University Medical College.

Henry V. Howe, director of the School of Geology at Louisiana State University, will receive the Sidney Powers Memorial Medal for his work in general geology, stratigraphy and micropaleontology on 26 April at a meeting of the American Association of Petroleum Geologists in Atlantic City, N.J.

G. Fred Somers has returned to the University of Delaware after a year's leave, during which time he was visiting professor at the College of Agriculture, University of Philippines (Los Banos). At the University of Delaware he has been appointed chairman of the department of biological sciences, School of Arts and Sciences.

Victor C. Twitty, executive head of the department of biological sciences of Stanford University, has been elected president of the Western Society of Naturalists. He succeeds Herbert L. Mason of the University of California.

Heinz A. Lowenstam, professor of paleoecology at California Institute of Technology, will discuss skeletel properties and paleoecology as a Sigma Xi national lecturer at a number of colleges and universities, from 8 February to 4 March.

Paul A. di Sant'Agnese has been named director of research in cystic fibrosis, celiac diseases, and allied disorders at the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., and clinical professor of pediatrics at Georgetown University Medical School. He was formerly on the staff at Babies and Presbyterian hospitals in New York City and assistant professor of pediatrics at Columbia University College of Physicians and Surgeons.

Louis E. Wise of the Institute of Paper Chemistry will receive the 1960 medal of the Technical Association of the Pulp and Paper Industry, in February.

Morris Cohen of the National Research Council, Ottawa, Canada, will receive the Willis Rodney Whiting Award of the U.S. National Association of Corrosion Engineers in Dallas, Tex., on 14 March for his work on the physical chemistry of corrosion.

Harold W. Mohrman, director of research-associated interests for the plastics division of Monsanto Chemical Co., has become director of research for the company's overseas division. He will coordinate the research of the company's foreign subsidiaries and affiliates with research of its domestic laboratories.

Henry J. Gomberg, assistant director of the Phoenix project of the University of Michigan since 1951, has been appointed director of the project—the university's research program in the peaceful uses of atomic energy. He succeeds **Ralph A. Sawyer**, vice president for research and dean of the graduate school.

Edwin S. Burdell, who will retire from the Cooper Union for the Advancement of Science and Art with the title of president emeritus, on 29 February, will become president of the Middle East Technical University of Ankara, Turkey, on 15 March. The United Nations Educational, Scientific, and Cultural Organization invited him to accept this position. He is to organize the English-language institution into a learning center similar to an American land-grant college.

At Cooper Union he incorporated the humanities and social sciences into the curricula of the School of Engineering and the Art School and strengthened the free adult education program.

William C. Leone, manager of the industrial systems division of Rheem Manufacturing Co., has been named vice president and general manager of Rheem Califone Corp., Los Angeles, Calif.

Recent Deaths

Ivan P. Bardin, Moscow, U.S.S.R.; 76; vice president of the Soviet Academy of Sciences; chairman of the Soviet committee for the International Geophysical Year; pioneer in developing the Soviet steel industry.

John L. Bremer, Boston, Mass.; 85; Hersey professor emeritus of anatomy at Harvard Medical School; researcher on the relationship of embryonic development to infant malformation; 25 Dec.

Alexander W. Evans, New Haven, Conn.; 91; emeritus Eaton professor of botany and curator of the Eaton Herbarium at Yale University; specialist in lichens and the Hepaticae; 6 Dec.

Cyrus E. French, White Plains, N.Y.; 44; chief of nutrition for the United Nations Children's Fund; former professor of nutrition at Pennsylvania State University; 3 Jan.

Aaron Himmelstein, New York, N.Y.; 45; cardiovascular surgeon; associate professor of surgery at Columbia University College of Physicians and Surgeons; contributer to cardiac-catheter research; 18 Dec.

Robert H. Oster, Baltimore, Md.; 58; professor of physiology at the University of Maryland School of Dentistry, where he helped establish the electroencephalograph laboratory; 2 Jan.

Lewis Pokras, New Hyde Park, N.Y.; 43; associate professor of chemistry at the Polytechnic Institute of Brooklyn; specialist in the chemistry of complex ions in water solutions; 24 Dec.

Edward Weiss, Philadelphia, Pa.; 64; pioneer in psychosomatic medicine; professor of clinical medicine at Temple University's School of Medicine; research director of the psychosomatic research fund of the National Committee on Mental Hygiene; 13 Jan.

Erratum: In the report, "All-female strains of teleost fishes of the genus *Poeciliopsis*" by R. R. Miller and R. J. Schultz [*Science* **130**, 1656 (1959)], the first names cited in references 3 and 4 are incorrect. The citation in reference 3 should have been C. Hubbs; that in reference 4 should have been C. L. Hubbs.

Erratum: In the April 1960 list of Forthcoming Events [*Science* **131**, 169 (15 Jan. 1960)], the date of the symposium on microbial reactions in marine environments is given incorrectly as 20–24 April 1960. This symposium is being held in 1961.

Book Reviews

Radiation, Genes, and Man. Bruce Wallace and Th. Dobzhansky. Holt, New York, 1959. xii + 205 pp. Illus. $3.50.

Over the past five years there have been frequent public debates by scientists about the damaging consequences of the exposure of our store of human genes to atomic radiations. The emotions aroused, to say nothing of the seemingly contradictory statements made, have probably left more people confused than were left either reassured or with heightened apprehension. This confusion is partly because there are many sources of such radiation, and it is not clear to most persons whether the damage is greater from medical and dental exposures, from industrial hazards, or from the fallout occurring after the testing of nuclear weapons. Confusion is even more definitely attributable to the fact that different "authorities," in good conscience, can speak reassuring words or raise their voices in alarm, when looking at the same facts. And it is partly because there are so many gaps in our present scientific knowledge of how much radiation we are exposed to, internally and externally, how many mutations might result, how harmful these mutations might be, on the average, and what the consequences are to an entire population, as well as to particular individuals, from a given degree of exposure. Two well-known geneticists, Bruce Wallace, of Cornell University, and Theodosius Dobzhansky, of Columbia University, have set out to clarify these matters for the general, nonscientific reader. No two persons could in all respects—scientific knowledge of these matters, ability to write clearly and interestingly, and their own participation in the exploration of these questions—be better qualified to perform such a task.

The book, however, quickly exposes the dilemma which faces everyone who undertakes to explain about the genetic hazards of nuclear radiations. The first five chapters, which provide the necessary general background of the subject, are as elegant and clear a statement as could be desired. The titles of these chapters sufficiently indicate their content: "Atomic energy—friend or foe?"; "Heredity, environment, genes and chromosomes"; "Spontaneous mutation"; "Atoms and radiations"; and "Induction of mutation by radiation."

Good diagrams and interesting examples aid greatly in the exposition of the subject. An exception is possibly the world map (pages 72–73) which attempts to show the heaviness of fallout at different latitudes by the *widths* of shaded bands placed at every 15° of latitude from the equator to the poles. This representation might lead some unwary readers to suppose that fallout descends in a peculiar banded pattern, since the real meaning of the widths of the bands is insufficiently explained.

By far the most significant part of the book is comprised by the next three chapters, which are entitled respectively "Genes in Mendelian populations," "Genetic effects of radiation on populations," and "Some unsolved problems." Here most readers will find hard going. Not that the same care has not been given to clear exposition—but the subject itself is not easy at first acquaintance. A certain amount of mathematical treatment cannot be avoided. And especially, some of the concepts, such as "genetic death," have meanings not to be inferred from the ordinary ones. Thus, "genetic death" is not the death of any person—it is the extinction of a gene from the population; and this, while it might occur through the death of its bearer before it is passed on to some child, may also occur because of the bearer's sterility, relative infertility, or even because by chance, and chance alone, the gene in question fails to be handed on to any of the living children of the bearer. (The latter is not uncommon in a species such as ours, where the size of the average family is quite small.) In spite of all such difficulties, the reader must be urged to plow manfully on, for the principles of population genetics explained here are the very heart of the matter.

It is encouraging that Wallace and Dobzhansky have not hesitated to tackle one of the moot issues involved in the assay of radiation-inflicted damage upon genes and chromosomes. This is the question of whether the human species is so highly selected and so well-adapted a species that all mutations which cause a departure from the "norm" can be regarded as unfavorable and are present in human populations only because fresh mutations keep replenishing their supply as fast as they are eliminated by "genetic death," or whether, on the contrary, there are many genes which are maintained in human populations because when heterozygous (that is, when carried in a single dose) they may confer some benefit, even though any individual who is homozygous for the same gene (that is, carries a double dose of the mutant) may be at a disadvantage in the process of natural selection. A good example is the mutant gene for sickle cell hemoglobin, which in the double dose produces a severe anemia from which the bearers commonly die fairly early in life. But normal hemoglobin is more avidly attacked by the plasmodium of tertian malaria than is sickle hemoglobin, so that in areas of Africa where malarial infections are severe, almost the only adult survivors are persons who have one dose of normal hemoglobin and one dose of sickle hemoglobin. The major question is: how common are such relationships between alternative sorts of genes in the human species? The authors are well known among geneticists as being strong proponents of the latter view; while H. J. Muller and others strongly advocate the former theory.

It is greatly to the credit of Wallace and Dobzhansky that they discuss this question with calmness and balance, and do not overadvocate their own position. In any case, as they strongly emphasize, when it comes to a matter of those mutations induced by high-energy radiations rather than mutations that arise spontaneously, there is every reason to regard the mutations as overwhelmingly harmful. Atomic radiations are not gentle agents. They smash chromosomes and mutate genes in a far more destructive way than do the normal causes of mutation, other than the background radiation that none of us can altogether escape.

A question of great importance which

the authors discuss is whether a continuing heavy exposure to radiations may actually cause the extinction of human populations, over and above the consequences in the form of increased numbers of defective individuals. Their answer to this question is on the reassuring side. This is because the 400- to 500-roentgen dose which is sufficient to cause death in half the exposed persons tends to preclude exposure to the very much larger doses it would take to extinguish the population because of whatever dominant lethal mutations might be induced. This conclusion is based, however, on the assumption that human genes and chromosomes are not a great deal more sensitive to radiation than those of fruitflies; but this assumption may be questioned on the basis of the observed sensitivity to low doses of x-rays of human cells growing in tissue culture. It is furthermore too bad that, in appraising the total situation, the authors have neglected to emphasize the relative significance of medical and occupational exposures to radiation. The treatment becomes focused a bit too much on the effects of fallout and possible nuclear war, and not on the multiplicity of exposures that the nuclear age may bring with it.

Let the last word be one of high praise for the efforts the authors have made to clarify a debate often marked by more heat than light. They bring out in their final conclusions the inescapability of making value judgments —far more political in nature than scientific—respecting the relative damage done by fallout and the desirability of a cessation of weapon testing. They point out the deficiencies in our present knowledge as well as the fact that radiation damage to living things is not all genetic damage. They take hope in the fact that mankind has acquired in its evolutionary progression not only a particular genetic heritage but also a means of passing on knowledge and of growing in wisdom through experience. They hope, therefore, that our species will surmount this threat to its continuance even as it has survived the lesser threats of the past. Unquestionably, this is the finest book yet published in the sharp debate over the genetic damage done by nuclear radiations. May it have many readers, and may each one cope manfully with its difficulties until he concludes its final page! He will be amply repaid.

BENTLEY GLASS
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Johns Hopkins University

This Sculptured Earth: The Landscape of America. John A. Shimer. Columbia University Press, New York, 1959. xii + 255 pp. Illus. $7.50.

Americans yearly become more and more travel minded, and John Shimer has written *This Sculptured Earth* for the increasing legions of men and women now criss-crossing the United States.

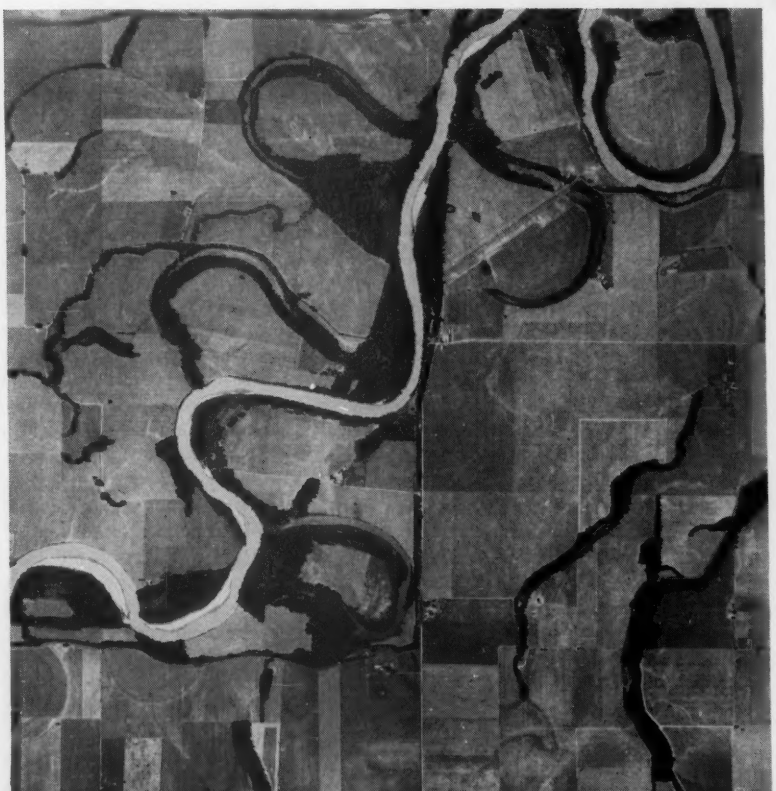
So this is a travel book. But it will not tell the traveler where to find a motel with a swimming pool, a gourmet's dinner, or an out-of-the-way antique shop. It won't tell the wayfaring American the shortest distance from here to there. But it will tell him how to look at the American landscape.

As we become a nation of travelers, we forget that our landscape has beauty and majesty, that it has a past and a future, that it can evoke awe and wonder, that it can provide inspiration and solace. John Shimer is trying to remind those of us who have forgotten—and tell those of us who have never known —that the physical land mass of the United States is something more than a barrier dividing the Atlantic and Pacific Oceans. To Shimer it is a landscape to be seen, to be understood, to be appreciated, to be treasured.

The author has managed to describe and to explain a vast amount of the physical geography of this country. Are you going to Boston? Then why is there a harbor there, and whence came the islands that dot the bay? Will you know the explanation of the towering Tetons as you drive by them on your way to Jackson Hole, Wyoming? Or (on a more intimate scale) will you understand that ridge of hummocky land that you speed over on the Indiana Turnpike near South Bend?

Shimer does more than describe. He gives us some idea of the vastness of time and the complexity of history behind the American landscape. He even gives us, in places, a glimpse of what another traveler might see in some far future eon.

The book contains a minimum of technical jargon. Needed terms are defined, and most of these appear again in a useful little glossary illustrated with neat line drawings by the author's wife, Florence Henry Shimer. Florence Shimer has also contributed some effective,



Meanders of the White River, Indiana.

simple drawings to the text. These supplement very nicely some 70 photographs, many of which are superb. One by Laurence Lowry, showing the eastern end of Martha's Vineyard, Chappaquiddick Island, Nantucket Sound, Cape Cod, and Massachusetts Bay, is on the cover of this issue of *Science*; another, showing the meanders of the White River near Edwardsport, Ind., is reproduced with this review.

SHELDON JUDSON
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Free Associations. Memories of a psychoanalyst. Ernest Jones. Basic Books, New York, 1959. 264 pp. $5.

The author of this book, Ernest Jones, was one of the principal contributors to, and developers of, the psychoanalytic theory of personality organization and function. This small and somewhat fragmentary autobiography was interrupted by his death in 1958.

Whatever one's personal views of psychoanalysis as a discipline may be, and I am favorably inclined towards it, Jones' somewhat abbreviated autobiography has severe limitations. Perhaps some of this reaction has to do with the level of expectation with which I approached the book and my subsequent disappointment in it.

It is likely that Jones' reminiscences about his early years will be a matter of interest to his intimates and to those who attach a sentimental significance to him, but they have little to recommend them to the general reader. Because his self-revelations are so fragmentary they do not provide the broad view which one would need in order to obtain a better understanding of the man. While the book is titled *Free Associations*, unfortunately the content is neither free enough to give the reader a reasonable sense of the scope of the man, nor disciplined enough to give the associations an inner coherence. This stands in striking contrast to Jones' earlier contributions to the theory and practice of psychoanalysis, which are marked by his logically consistent and definitive style.

For those who have a particular interest in the development of psychoanalysis as a "movement" (although Jones deplored the widespread use of this term), the latter part of this book has many pertinent historical references. One is impressed by Jones' enthusiasm for the newly developed perspective of personality development, and by the intensity of his drive to communicate the findings to others. The violence of his response to views which deviated from the classically psychoanalytic ones is one of the more remarkable aspects to be observed. These responses are presented with a degree of candor which, while it is hardly one of the more flattering aspects of psychoanalysis, throws light on the impact of radically new ideas in any sphere of science. Such new ideas are significant, among other ways, both as things in themselves and as disrupters of the usually definitive social hierarchy within a given field of endeavor. Then, of course, as the new system of ideas becomes intrenched, it in turn establishes its own hierarchal structure.

SAMUEL NOVEY
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Handbuch der Physik. vol. 44, *Nuclear Instrumentation*, I. S. Flügge, Ed. Springer, Berlin, 1959. vii + 473 pp. Illus. DM. 125.

"Nuclear Instrumentation on a Grand Scale" would be an appropriate title for volume 44 of the *Handbuch der Physik*, which is titled simply *Nuclear Instrumentation*, I. The articles contained here describe the major pieces of nuclear physics instrumentation, the heavy machines most commonly associated with modern experimental physics.

One does not blindly set out to build devices such as are described in these eight articles, and as a consequence, the most interested reader will already be familiar with the general theoretical discussions presented here. It is the specific comments about specific machines that make these articles most lively; the lore of machine building is well represented in this volume of the *Handbuch*.

The first article, by E. Baldinger, presents a thorough treatment of rectification circuits and then discusses cascade generators. R. G. Herb's discussion of Van de Graaff accelerators contains some sage advice for the would-be builders of such machines who would also like to work in experimental physics: "A faithful copy of a generator that is operating can be safely predicted in regard to performance." And conversely!

The magnetic accelerators—cyclotrons and synchrocyclotrons, electron synchrotrons, and betatrons—are discussed by Bernard L. Cohen, Robert R. Wilson, and Donald W. Kerst. Cohen's article contains an interesting tabulation of the characteristics of a large number of cyclotrons and an excellent treatment of the theory and the headaches (the practice) of cyclotron construction and operation.

George K. Green and Ernest D. Courant (Brookhaven National Laboratory), have written a monumental article on proton synchrotrons; they draw heavily on the experience with the Brookhaven, University of California Radiation Laboratory, Birmingham, and Dubna machines. The design features of the alternating gradient synchrotrons at Brookhaven National Laboratory and at the laboratory of the European Organization for Nuclear Research (CERN) are outlined. The latter is now in operation.

Linear accelerators—electron, proton, and heavy ion—are discussed by Lloyd Smith. An article by D. J. Hughes contains selected topics on reactor techniques of particular interest to nuclear physicists.

Very little of the material in these articles will interest those experienced in the design and operation of "his machine," except for comparison purposes. These articles will be of great use to those who wish to be brought up to date on machines with which they are not well acquainted.

JOHN D. FOX
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Florida State University

The Gentle Art of Mathematics. Dan Pedoe. Macmillan, New York, 1959. 143 pp. Illus. $3.50.

This is a book for the intelligent layman who wants to know something about modern mathematics and is willing to work a little to attain this knowledge. It starts out entertainingly enough with a discussion of mathematical games. These are used to acquaint the reader with number systems other than the familiar decimal system, although their use in electronic computers is not even mentioned. The next chapter discusses the theory of probability and its many opportunities for paradox. More paradoxical ideas are introduced in the following chapter, which discusses infinity and introduces

transfinite numbers. At this point, a breathing spell is offered with a rather trivial chapter on logic. But the author returns shortly to serious mathematics with a discussion of various topics in topology. Abstract algebra is then introduced, with an aside on the esthetics of mathematical symmetry, and this is followed by a discussion of infinite series. The foundations and essentials of mathematics are examined in the concluding chapters.

Although there is some new material, presented rather pleasantly, one has the impression that he has seen most of this before in some other popular treatment of mathematics. In addition, there are other failings; these include a very detailed table of contents that promises more than it delivers and several errors, some rather serious. Thus, the explanation of when one class has a greater transfinite number than another class (page 58) omits a crucial clause, and the discussion of bracketing in infinite series (page 126) is slightly misleading. Finally, I wonder how insulted the people at the University of North Carolina will be by his statement that extrasensory perception is investigated there, instead of at neighboring, rival Duke.

PHILIP RABINOWITZ
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Fresh-Water Biology. Henry Baldwin Ward and George Chandler Whipple. W. T. Edmondson, Ed. Wiley, New York; Chapman and Hall, London, ed. 2, 1959. xx + 1248 pp. Illus. $34.50.

Perhaps no field and laboratory identification manual in the English language has been so widely used as the original edition (1918) of "Ward and Whipple." Our knowledge of fresh-water invertebrates has increased so markedly, however, especially during the past 25 years, that this complete revision is long overdue. The general organization of the first edition has been followed; that is, each chapter is written by a specialist and is devoted to a particular taxonomic group. The material consists mainly of illustrated keys to those fresh-water forms found north of the Rio Grande. Beyond introductory remarks, little space is usually devoted to a consideration of the *biology* of the groups discussed. Depending on the complexity of the group and the degree to which it is known in North America, each key is usually carried to either genus or species. The former situation, for example, applies to the Protozoa, Bacteria, Fungi, most of the Algae, Nemata, Rotifera, Insecta, Acari, and Bryophyta. The latter arrangement includes such groups as the Myxophyceae, Porifera, Gastrotricha, Bryozoa, Tardigrada, Oligochaeta, Hirudinea, Crustacea, and common vascular plants.

Most of the 46 chapters contain many fresh illustrations, but for the Rhizopoda, Actinopoda, Porifera, Nemata, Oligochaeta, Hirudinea, Cladocera, and Mollusca the majority of the illustrations are those of the first edition (reproduced, apparently, from the old, worn plates). There are no halftones.

Although the editor, W. T. Edmondson, has done a good job of reconciling the inequalities in style, emphasis, illustration, and conviction of the contributors, there are important differences in the level of usefulness of the various presentations.

Many readers will be disappointed to find that vertebrates and internal parasites are not included, but, on the other hand, new and excellent chapters on the Fungi, Tardigrada, Polychaeta, and Bryophyta have made their appearance. In addition, the chapters on aquatic insects have been greatly expanded, although they no longer include terrestrial adult forms having immature aquatic stages. Other taxonomic groups given greatly revised and expanded treatment are Bacteria, Algae, Protozoa, Gastrotricha, phyllopods, Ostracoda, Copepoda, Malacostraca, Acari, and rooted aquatics. The brevity of the final chapter, on "Methods and equipment," however, is regrettable. There appear to be very few typographical errors.

The editor has been intentionally conservative in making up the index, but many biologists will feel that this is a serious error. The following terms, for example, are used in the text and keys but are not to be found in the index: *birotulate, cingulum, crawling water beetles, microsclere, operculum, paralabial plate, theca, trichocyst, trochus, water tiger,* and *whirligig beetle.*

Although specialists will disagree on matters of emphasis and taxonomy, there will be no argument as to the care and labor involved in the preparation of this book. Edmondson has done aquatic biology a great service in providing direction and stimulus for 50 other specialists in the preparation of the compilation, and in editing their efforts.

The high price is most unfortunate. Undoubtedly much of the cost is a reflection of the complicated (sometimes wastefully complicated) format.

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Department of Biology, University of Colorado

New Books

Antibiotic Therapy for Staphylococcal Diseases. Henry Welch and Maxwell Finland, Eds. Medical Encyclopedia, New York, 1959. 220 pp. $4.50.

Arterial Embolism in the Limbs. The clinical problem and its anatomical basis. A. L. Jacobs. Livingston, Edinburgh, Scotland, 1959. 212 pp.

Automatic Titrators. J. P. Phillips. Academic Press, New York, 1959. 233 pp. $6.

Automating the Manufacturing Process. George F. Hawley. Reinhold, New York; Chapman and Hall, London, 1959. 156 pp. $4.95.

Calculus with Analytic Geometry. Donald E. Richmond. Addison-Wesley, Reading, Mass, 1959. 473 pp. $8.75.

The Cathode-Ray Tube. And its applications. G. Parr and O. H. Davie. Reinhold, New York, ed. 3, 1959. 445 pp. $9.50.

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Reports

Enzymatic Basis of Mannose Toxicity in Honey Bees

Abstract. Honey bees have a negligible amount of phosphomannoseisomerase, together with a high content of a hexokinase which phosphorylates mannose more efficiently than fructose or glucose. Competition at the phosphorylation level plus accumulation of mannose-6-phosphate can fully account for the toxicity of mannose in honey bees.

In the course of a thorough investigation on the sense of taste in honey bees, von Frisch (*1*) incidentally found, 30 years ago, that mannose was strongly toxic for honey bees.

Mannose is a common and widely utilizable hexose, which is known to be metabolized through the reactions:

$$\text{Mannose} + \text{ATP} \rightarrow \text{mannose-6-P} + \text{ADP} \quad (1)$$

and

$$\text{Mannose-6-P} \rightleftarrows \text{fructose-6-P} \quad (2)$$

Reaction 1 is catalyzed by hexokinase, an enzyme common to glucose, mannose, and fructose (*2*), which is widely distributed (*3*). Reaction 2 is catalyzed by phosphomannoseisomerase (*4*), which also is of wide occurrence (*5*). The work presented in this report shows that honey bees have a high content of hexokinase, while they have no more than a trace of phosphomannoseisomerase.

Worker honey bees (*Apis mellifera*) were obtained from local sources (*6*) and maintained on honey until used. A number of trials with different batches consistently confirmed the toxicity of mannose. In parallel experiments, lots of about 20 bees each were offered 1*M* mannose, water, and 1*M* glucose, respectively. Of those offered mannose, 50 percent died within 1.5 hours, and over 90 percent, within 3 hours, at which time more than 90 percent of the controls (those given water) still survived. Within 12 hours over 90 percent of the controls had died, as against less than 10 percent of the honey bees given glucose.

For the exploration of enzymes, bees fasted for 1 hour were killed by freezing at −20°C. The frozen bees were homogenized in a Waring blender for 2 minutes with 4 volumes of cold 0.005*M* ethylenediaminetetraacetic acid neutralized to *p*H 7. The suspension was freed of residual pieces of hard tissue by squeezing through two layers of gauze. The clarified homogenates were used without delay or were stored frozen until assay. The results in Table 1 show a high phosphorylation activity toward glucose, mannose, and fructose, as well as strong inhibition of the activity toward fructose by both aldoses, a high phosphoglucoseisomerase activity, and a barely detectable trace of phosphomannoseisomerase activity.

These results indicate a hexokinase common for glucose, mannose, and fructose. This conclusion is supported by the following complementary observations: competitive inhibition of the three hexoses by N-acetylglucosamine and phosphorylation of 2-deoxyglucose and glucosamine. Inhibition by glucose-6-P tends to lower the apparent phosphorylation rate of glucose with respect to that of mannose. Nevertheless, even under conditions of minimal product accumulation, the maximal phosphorylation rate of mannose appears to be as high as 1.7 that of glucose, while the apparent affinities are similar (Michaelis constants about 1×10^{-4} *M*) (*8*).

Phosphoglucoseisomerase is in excess over hexokinase. This fact has been repeatedly observed even in tissues where glycolysis proceeds from free hexose rather than from glycogen. Nevertheless this must not be interpreted as a superfluous excess. Owing to the free reversibilty of the reaction catalyzed by the phosphoglucoseisomerase, the enzyme must be "in excess" to create sufficient net activity within the glycolytic chain without requiring levels of glucose-6-P which could seriously disturb normal metabolism.

This excess makes more obvious the insufficiency of the phosphomannoseisomerase in bees. The highest value found has been less than one-tenth of the mannose phosphorylating capacity. At these low levels of activity it is difficult to ascertain to what extent there is any true phosphomannoseisomerase at all in honey bees. Among other considerations there is the possible contribution of enzymes from microorganisms when whole, normally raised bees are used.

These results indicate that the mannose toxicity in honey bees is a metabolic disease due to lack of balance between hexokinase and phosphomannoseisomerase, presumably due to mutational loss of the ability to make the latter. Mannose would both competitively inhibit glucose and fructose phosphorylation and give rise to an accumulation of mannose-6-P which could interfere with glycolysis in a number of ways; it is a competitive inhibitor of phosphoglucoseisomerase (*9*). Both the high hexokinase content and the speed with which intoxication by mannose occurs must be related to the fact that honey bees are markedly dependent for activity on a high blood-sugar level, which in turn depends on recent food intake (*10*). This metabolic disease bears analogies to the galactosemia syndrome (*11*) and to the experimental interference with glucose metabolism by 2-deoxyglucose (see *12*).

An exploration of mannose toxicity and phosphomannoseisomerase, or of phosphomannoseisomerase alone, in other bees and eventually in other Hymenoptera could give interesting clues to the genetic relationships among closely related species.

Table 1. Hexokinase and phosphohexoseisomerases in honey bees.

Substrate	Activity (μmole/gm/15 min at 30°C)		
	Phosphorylation*		Isomerization†
	Sugar	Ketose	
Glucose	105		
Mannose	190		
Fructose		100	
Fructose + glucose		35	
Fructose + mannose		20	
Glucose-6-phosphate			700
Mannose-6-phosphate			About 1‡

* Estimated by substrate disappearance essentially as described by Crane and Sols (*3*), 0.1 ml of homogenate and 3 μmole of substrate (plus 6 μmole of the second substrate in the fourth and fifth experiments) being used, in a total volume of 0.5 ml. † Studied by ketose formation with the borate method of Alvarado and Sols (*7*), 0.01 to 0.1 ml of homogenate in a total volume of 0.4 ml and incubation times of from 10 minutes to 2 hours being used. ‡ Values from about 0.3 to 10 were obtained in different experiments.

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* **125**, 16 (1957)].

Note added in proof. After the preparation of this report, our attention has been called to a paper from von Frisch's department, in which the results of an exploration of mannose toxicity in a number of insects are reported [T. Staudenmayer, *Z. vergleich. Physiol.* **26**, 644 (1939)]. Mannose was to be toxic to several apidae examined and to *Vespa vulgaris*, but not to other Hymenoptera.

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Identity of a Rust on Ephedra

Abstract. The aecial stage of a rust on *Ephedra* has been called a *Peridermium*. Clues as to its telial stage have been lacking. It is here described as resembling more a form of *Roestelia*, and the reasons for its possible relation to *Gymnosporangium multiporum* Kern are presented: the two sets of hosts have similar distributions: the two rust stages have the same geographic range; they have been found in close proximity in the field.

Ephedra is a genus of the joint-fir family (Ephedraceae) distributed over the arid regions of the northern hemisphere. The drug ephedrin, administered as an astringent, is obtained from a Chinese species. The small scale-like leaves and jointed stems of these plants make them resemble somewhat the horsetails. Botanically the joint-firs are classed with the gymnosperms, which bear naked seeds in contrast to the angiosperms, with seeds enclosed in an ovary. The joint-fir family has points of agreement with both Gymnospermae and Angiospermae, making the group in some ways an intermediate one between the two classes.

A rust fungus (order Uredinales) has been known as a parasite on species of *Ephedra* since 1877. This rust has been reported as, "A common and conspicuous species along the southwestern border of the United States and southward into Mexico" (*1*). It is usually listed as *Peridermium ephedrae* Cooke (*2*). In the Natürlichen Pflanzenfamilien, Dietel referred to it as *Aec.* [*Aecidium*] *Ephedrae* Cke. (*3*).

This rust on *Ephedra* is an aecial (or aecidial) stage only, and without a known perfect (telial) stage can be referred only to a form genus. *Peridermium* is a form genus name for various aecia on gymnospermous hosts, whose telial connections are unknown. Many of the forms temporarily placed here have been connected to telial stages. All of these aecial forms have been on coniferous hosts (order Coniferales), and their telial stages belong to the rust family Melampsoraceae.

The *Ephedra* rust doubtless has been called a *Peridermium* chiefly because the host is classed as a gymnosperm. *Ephedra*, however, is not a conifer and the aecial stage on it is in certain respects unlike the forms of *Peridermium* on these hosts.

It more closely resembles some of the highly differentiated species of the form genus *Roestelia*, in which the peridium (outer coat or investment of the sorus) is cylindrical, elongated (up to 5 mm), and dehiscent at the apex. For many years the forms of *Roestelia* were believed to have a restricted host range: species of the tribe Pomeae or family Malaceae (depending on the classification used). We now know that a few species with *Roestelia*-like aecia in habit not only Malaceae but other families—Rosaceae, Hydrangiaceae, Myricaceae—belonging to the angiosperms. These rusts are heteroecious and those for which a telial stage is known belong to the genus *Gymnosporangium*. Without exception species of *Gymnosporangium* have their telial stages on the family Juniperaceae which is a part of the Gymnospermae. Here we have heteroecious rusts alternating between angiosperms and gymnosperms.

We are now strongly suggesting that the rust on *Ephedra* is a *Roestelia* and that it is the aecial stage of a *Gymnosporangium* on a *Juniperus* species. We are aware that this will create an anomalous situation. It will be the first case where aecial and telial stages of a heteroecious rust inhabit two families both belonging to the Gymnospermae. Perhaps this may be regarded as supporting the view that the *Ephedra* family is not truly gymnospermous, as has been pointed out by some taxonomists.

The species of *Gymnosporangium* believed to be the telial stage of the *Ephedra* aecial stage is *G. multiporum* Kern (*4*). The geographical range of these two stages is essentially the same. The similar distribution of the two sets of hosts—the various species of *Ephedra* and *Juniperus deppeana* Steud. (*J. pachyphlaea* Torr.), *J. monosperma* (Engelm.) Sarg., and *J. osteosperma* (Torr.) Little [*J. utahensis* (Engelm.) Lemmon]—and their association on desert lands make possible the harboring of a fungus which must pass from one set to the other. This lends credence to the suggestion that *Gymnosporangium multiporum* is the telial stage of the *Ephedra* rust. Not only do the ranges and distribution of these rust stages and of their hosts favor this conjecture, but there is additional evidence from field observations. *Gymnosporangium multiporum* and the aecia on *Ephedra* have been found in proximity in an area of the South Rim of the Grand Canyon, Coconino County, Arizona. Our prediction is made with much confidence. Proof can be had only through cultures, involving inoculations under controlled conditions.

It is pertinent to note that there are numerous collections of the rust on *Ephedra* but that there has been no suggestion till now of a possible telial stage. *Gymnosporangium multiporum* is so inconspicuous as to elude easy detection even when present. Relatively few collections of *G. multiporum* have been made. In any event its collectors would doubtless have sought *Roesteliae* on Malaceae (the usual alternate stages for *Gymnosporangium*) and naturally would have disregarded the *Ephedra* as being of no concern. These facts may help explain why the present hypothesis has not been suggested sooner (*5*).

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17 August 1959

Cosmic Neutrino Radiation

Abstract. New and more powerful methods for eliminating background intensity are needed in order to make possible the development of neutrino astronomy into a new, far-reaching branch of science.

In a recent paper F. Reines and C. L. Cowan mentioned the future possibility of detecting the cosmic neutrino flux reaching the earth (*1*). We wish to present a more quantitative picture of this most penetrating radiation of the universe.

Today experimental technique makes possible the detection of a reactor antineutrino flux of intensity $\Im = 10^{13}$ ν cm^{-2} sec^{-1} in the energy interval 2 to 6 Mev with satisfying accuracy; this corresponds to a reaction rate of $\Im\sigma \cong 10^{-30}$ ν sec^{-1} per nucleus. Reines and Cowan (*2*) made use of the reaction

$$\nu + p \rightarrow n + e^+ \qquad (1)$$

(energy threshold 1.8 Mev). A neutrino flux may also be detected, with roughly comparable accuracy, by making use of the Pontecorvo-Davis reaction (*3*):

$$\nu + Cl^{37} \rightarrow Ar^{37} + e^- \qquad (2)$$

(energy threshold 0.8 Mev). It is hoped that the detection threshold can be lowered in the near future by one or two orders of magnitude, without extensive modification of the experimental method (*4*).

Apart from nuclear reactors, the sun is the most intensive source of neutrinos for laboratory observations; several percent of its energy production is carried off by the neutrino current ($\Im > 10^{10}$ ν cm^{-2} sec^{-1} at the earth). If the fundamental fusion process taking place in the central part of the sun is the C-N cycle, the β^+ activity of the isotopes N^{13} and O^{15} has to be taken into account as a source of neutrinos. Since the energy spectrum of these nuclei is known, the average cross section of reaction 2 is theoretically computable: $\sigma = 10^{-43}$ cm^2, and this results in a reaction rate $\Im\sigma \cong 0.6 \times 10^{-82}$ ν sec^{-1}. If, however, the fundamental energy-producing process of the sun is direct H-D fusion, ending in

$$He^3\,(He^3, 2p)\,\alpha$$

the energy of the neutrinos originating from the reaction

$$2p \rightarrow D + e^+ + \nu$$

lies lower than the threshold for the entire capture reaction (reaction 2), and consequently $\Im\sigma = 0$ (Fig. 1) (*5*).

According to the recent suggestion of W. A. Fowler (*6*), another possibility for completion of the H-D chain is

$$He^3\,(\alpha, \gamma)\,Be^7\,(e^-, \nu)\,Li^7\,(p, \alpha)\,\alpha$$

and this supplies neutrinos with energy comparable to those of the C-N cycle. The second neutrino of this chain is of low energy, so one arrives at an unexpected reaction rate $\Im\sigma \cong 0.3 \times 10^{-82}$ ν sec^{-1}. It is possible, however, that the same chain is completed via

$$Be^7\,(p, \gamma)\,B^8\,(\beta^+\,\nu)\,Be^8\,(\alpha)\,\alpha$$

and the B^8 nucleus emits neutrinos with very high energy (end point at 14.1 Mev).

The abundance of this reaction depends on the (unknown) p capture cross section of Be^7. If the Be-B branch is supposed to give the whole energy production of the sun, with the calculated average neutrino capture cross section $\sigma = 2 \times 10^{-42}$ cm^2, one arrives at the high detection rate $\Im\sigma \cong 8 \times 10^{-82}$ ν sec^{-1}. It is to be expected that a detection threshold of $\Im\sigma = 10^{-82}$ ν sec^{-1} will be reached in a reasonable time; in this case one would be able to decide experimentally about the character of the fusion processes taking place in the inner part of the sun, and this would be equivalent to empirical determination of the temperature at the center. (Photons give us information—as a result of their smaller penetrating power—only about the surface temperature of the sun.)

It is impossible to find any difference between a distant celestial body built up from common matter and another one built up from antimatter (*7*) by observing their light, but in principle it would be possible to find a difference by observing their neutrino radiation (that is, $\gamma \equiv \bar{\gamma}$, $\nu \neq \bar{\nu}$). (A star similar to our sun is a neutrino-emitter, but a star built up from antiatoms would be an antineutrino-radiator.) Whether this possibility will become available seems very questionable today. The problem of the "neutrino telescope" is discussed below.

The result of the small capture cross section of the neutrino is that the mean free path of the neutrinos of the 1 to 10 Mev energy region in the universe amounts to about 10^{20} light-years (that of the antineutrino is a little less). From this it follows that neutrino radiation offers a very useful opportunity for observation of events very distant in space and time (in principle, up to 10^{20} light-years and 10^{20} years, respectively), provided, naturally, that the problem of detection can be solved. For example, the character and intensity of the neutrino radiation reaching the earth from outside the solar system are very sensitive indicators of the way in which the chemical elements are formed. If the universe can be considered to be in a steady state, and if the origin of heavier nuclei is connected with the fusion of hydrogen in stars, the average neutrino density has to be equal to the density of neutrons; thus, a flux of $\Im \approx 10^8$ ν cm^{-2} sec^{-1} is to be expected.

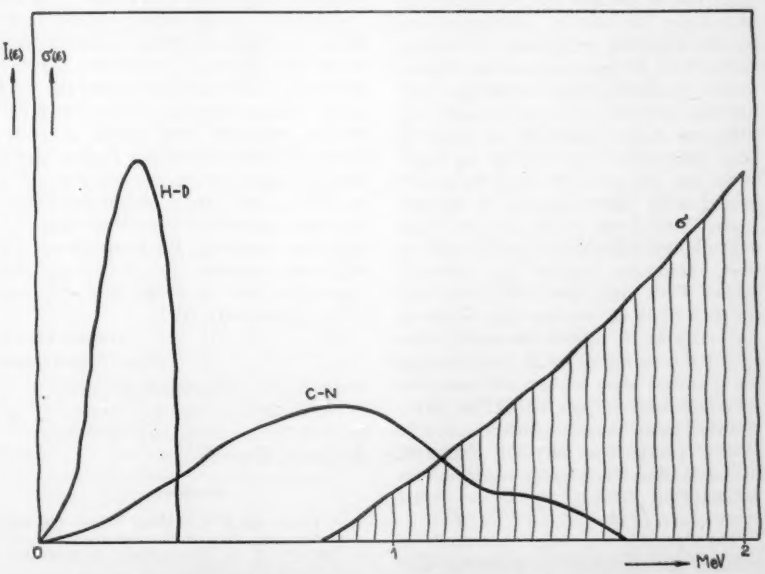

Fig. 1. Energy dependence of the cross section for neutrino detection and energy spectrum of neutrinos emitted in the H-D and C-N type fusion processes. (For the H-D-Be-B branch, the intensity becomes perceptible only above 2 Mev.)

The energy spectrum of this flux is similar to that of the sun, but in an expanding steady-state universe [suggested by the theory of Bondy and Gold (*8*)], the energy distribution is still lower as a result of the Doppler shift. One gets a reaction rate $\Im \sigma < 10^{-38}$ ν sec^{-1} for this flux, which is certainly a very small value. The antineutrino flux can be neglected.

If, on the other hand, the birth of heavy nuclei took place in an early, compressed state of the expanding universe, one would expect much more intensive neutrino radiation. In the highly compressed state of matter most of the nucleons had to be in a neutron-rich state, and during the formation of the proton-rich state of today, also an antineutrino flux of relatively high energy distribution and of relatively high intensity had to be emitted: $\Im \approx 10^{7}$ ν cm^{-2} sec^{-1} [that is, the density of the neutrinos has to be comparable to the proton density (*9*)]. This corresponds to a detecting reaction rate $\Im \sigma \approx 10^{-35}$ ν sec^{-1}. If the compressed state of matter were connected with a high temperature, a thermal neutrino and antineutrino radiation of considerable density also would have originated. Thermodynamic equilibrium between neutrinos and atoms can be attained in a state of nuclear density in microseconds; in a state of stellar density, in years; and in a state of the average density of today, in about 10^{80} years. This means that after a certain stage of expansion no interaction takes place any longer and the hot neutrino-antineutrino gas "freezes"; the intensity and spectrum of the gas are no longer regulated by the atomic interactions but by the adiabatic expansion. According to the laws of thermodynamics, experimental detection below a neutrino temperature of 10^{8}°K is not possible. An observed equal intensity of neutrino and antineutrino flux would be explicable on the basis of an origin connected with thermodynamical equilibrium. There seems to be only one other explanation: If celestial bodies built up from common matter and celestial bodies built up from antimatter are isolated from each other and occur in the universe in equal abundance—that is, if not only the physical laws but also the physical state of the universe are invariant with respect to PC transformation, being neutral with respect to electric charge and baryonic charge at the same time, the average neutrino and antineutrino density would be equal everywhere (*7*).

The answer to the question of whether the detection of neutrinos will make it possible to decide between the different cosmogonical views depends on whether the detection threshold attainable today, $\Im \bar{\sigma} = 10^{-50}$ ν sec^{-1}, can be diminished by several orders of magnitude. The most difficult problems of decisive importance are that of eliminating the much more dominant neutrino radiation emitted by the sun and that of the antineutrino flux of terrestrial radioactivity; this background intensity is of a greater order of magnitude than the cosmic flux to be detected. Neutrinos of high energy distribution are emitted in the atmosphere also by the decaying mesons generated by cosmic rays, but the total intensity of this radiation is nevertheless negligible as compared to the neutrino fluxes mentioned above. The anisotropic angular distribution of the electron emission in certain neutrino capture reactions would serve as a useful basis for the construction of a "telescope" differentiating neutrinos of terrestrial or solar origin and neutrinos of stellar origin, respectively. The differential cross section of the capture reaction is as follows:

$$\sigma(\theta)\, d\Omega = \frac{f^2}{16\pi^2\hbar^4c^3}\left\{\left|\int 1\right|^2\left(1+\frac{v}{c}\cos\theta\right)+\left|\int \sigma\right|^2\left(1-\frac{1}{3}\frac{v}{c}\cos\theta\right)\right\} pE\,d\Omega$$

where θ denotes the angle between the direction of the captured neutrino and the emitted electron. In the case of reaction 1, the angular dependence of $\sigma(\theta)$ does not exist, but, for example, for the pure Gamow-Teller transition

$$\nu + D \rightarrow n + n + e^{+} \qquad (3)$$

(energy threshold 4 Mev) one can draw conclusions about the direction spectrum of the incoming antineutrinos from the angular distribution of the positrons. Naturally this makes the telescope method applicable only for high-energy neutrinos and makes the possibility of detection much further away than is suggested by the accuracy $\Im \sigma = 10^{-30}$ ν cm^{-2} sec^{-1} obtainable today. Another possibility would be that offered by measuring the neutrino energy spectrum—namely, by comparing the absorption rates in nuclei with different energy thresholds.

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28 January 1959

Computer Analysis of Reflex Control and Organization: Respiratory Sinus Arrhythmia

Abstract. Respiratory sinus arrhythmia in waking man is described by differential equations which relate thorax circumference acceleration to instantaneous heart rate. Consequent experiments show that the arrhythmia is initiated by stretch receptors within the thorax rather than by hemodynamic or central factors, and that it is due mainly to superimposed biphasic inspiratory heart rate transients of about 15 seconds' duration. Analysis of respiration heart rate reflex provides a new quantitative physiological tool.

The changes in heart rate produced through changes in vagus inhibition, which accompany respiration, present both a varied and regular picture. The regularities appear as waves in the heart rate of the same frequency as the respiration. As a result of this regularity it has usually been assumed that a causal relation exists between inspiration and cardiac acceleration, and between expiration and deceleration (*1*). Certain investigators have observed, however, that the wavelike changes in the heart rate often show the opposite phasic relation to respiration (*2*). Recent work displays what appeared to look like a lag of one cycle between the respiration and the heart rate waves (*3*).

The irregularities in the heart rate trace have been difficult to relate to respiration. How much of the unwavelike and apparently irregular changes may be due to respiration as compared with other causes has remained undetermined. In order to investigate these conflicting results, we have applied the method of dynamic analysis as developed for automatic control system theory (*4*). Simulation by analog computer techniques, in experiments designed with the aid of control system theory, with unanesthetized human subjects, shows several results.

1) Two different biphasic reflexes are the main causes of changes in heart rate produced by respiration. One of these is produced only by inspiration and the other only by expiration. The two reflexes are both biphasic in the same direction. Each reflex first causes acceleration and then deceleration of the

heart rate. The time course of the reflex is of the order of 4 seconds for the accelerated phase and 10 seconds for the decelerated phase, making a total of 14 seconds for the complete transient. The expiration transient differs to some extent in shape from the inspiration transient, being usually of smaller amplitude and having a somewhat longer acceleratory phase, but it is in no way in the opposite direction from the inspiration transient, but clearly in the same direction.

2) The observed patterns of heart rate changes produced by respiration are the result of the superposition of biphasic heart rate transients which may or may not have time to complete themselves before the onset of the next transient. Because of the diphasic nature of these transients and the fact that both the inspiration and expiration are in the same direction, the wavelike patterns observed bear a different phasic relation to respiration depending on how fast the respiration rate is.

3) For respiration rates of about 4 per minute and slower, sufficient portions of the transients can complete themselves to give the effect of twice as many heart rate waves as respiratory waves. If one employs a method of step-wise breathing—that is, inspiration in several steps and likewise with expiration—then one obtains a biphasic heart rate transient for each step in respiration. In this way one can obtain any whole number relation between respiration and heart rate waves.

4) The time course of basic inspiration heart rate transients is independent of the degree of normal activity or rest, and thus of blood flow. The time course of the reflex in a given individual does not change regardless of initial heart rate.

5) Atropine in doses sufficient to reduce materially the amplitude of the heart rate transient (0.6 mg, intravenous) changes the time course of the transient, producing considerable slowing. As recovery from the effect of atropine takes place, the time course returns to its normal relationship and even temporarily becomes faster than the normal value of about 14 seconds. Both the time course of recovery and the extent of changes are dissimilar for the two reflexes.

6) Positive- or negative-pressure artificial respiration produces heart rate transients similar to those of natural respiration for similiar respiratory maneuvers.

7) Of 50 subjects tested, every one showed the two basic biphasic reflexes. Individuals showed considerable differences in amplitude and lesser differences in duration of reflex.

8) The mathematical expressions for the changes in vagus inhibition producing these heart rate changes are given by Eqs. 1 (for $dR/dt > 0$) and 2 (for $dR/dt < 0$).

$$\frac{\mathcal{V}}{\mathcal{R}} = \frac{-ks^2}{(1 + T_1 s)\ (1 + T_2 s)} \qquad (1)$$

$$\frac{\mathcal{V}}{\mathcal{R}} = \frac{k' s^2}{(1 + T_1 s)\ (1 + T_2 s)\ (1 + T_3 s)} \qquad (2)$$

These are the transfer functions relating changes in vagal inhibition to respiration. (Transfer functions are convenient means of handling linear, high-order differential equations in terms of Laplace transforms.) V is the vagal inhibition (as a firing rate) and R is the circumference of the thorax (the Laplace transforms of V and R are $\mathcal{V}$ and $\mathcal{R}$, respectively); s is the Laplace operator; T_1, T_2, and T_3 are time constants; and k and k' are sensitivity constants. The parameters for the inspiratory reflex are thus k, T_1, and T_2. For the expiratory reflex they are k', T_1, T_2, and T_3.

These transfer functions (Eqs. 1 and 2), written in the usual differential equation form, become Eq. 3 (for $dR/dt > 0$) and Eq. 4 (for $dR/dt < 0$)

$$\frac{d^2V}{dt^2} + \frac{T_1 + T_2}{T_1 T_2}\frac{dV}{dt} + \frac{V}{T_1 T_2} + \frac{k}{T_1 T_2}\frac{d^2R}{dt^2} = 0 \qquad (3)$$

$$\frac{d^3V}{dt^3} + \frac{T_1T_2 + T_2T_3 + T_3T_1}{T_1T_2T_3}\frac{d^2V}{dt^2} + \frac{T_1 + T_2 + T_3}{T_1T_2T_3}\frac{dV}{dt} + \frac{V}{T_1T_2T_3} - \frac{k'}{T_1T_2T_3}\frac{d^2R}{dt^2} = 0 \qquad (4)$$

Note that the respiration enters the equations only as a second derivative, or acceleration, of thorax circumference; the switching of equations depends on the sign of the motion.

The differential equation relating calculated vagus inhibition changes to heart rate is

$$\frac{1}{4\pi^2 r_0^2 - (V_0 + \Delta V)}\frac{d^2y}{dt^2} + y = 0 \qquad (5)$$

Parameter r_0 corresponds to the heart rate with complete absence of vagus inhibition, V_0 to the normal vagal tone, and ΔV the changes in vagal tone

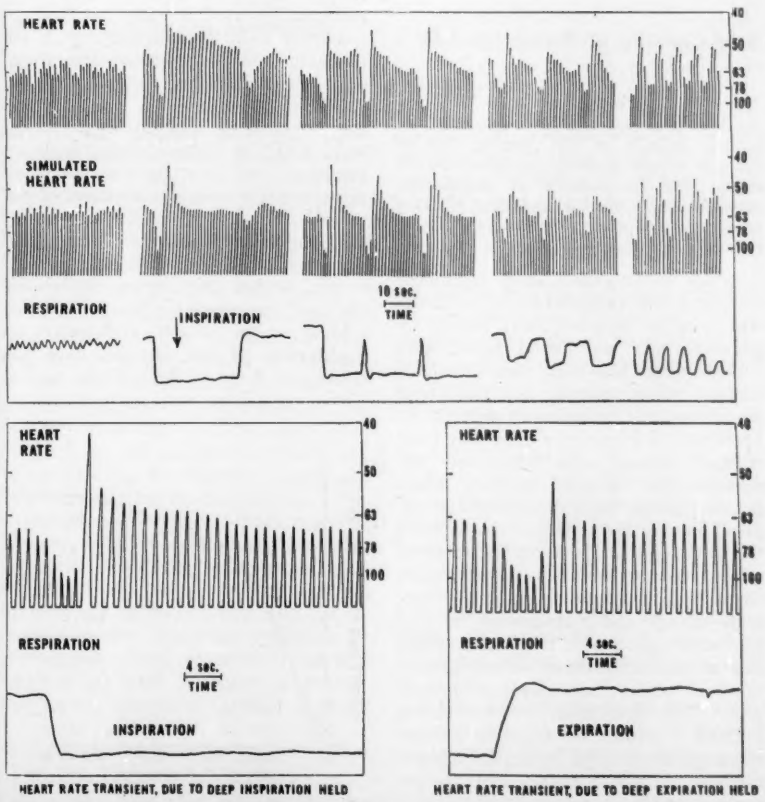

Fig. 1. Simulated and actual heart rate patterns for various modes of breathing; basic RHR (respiratory heart rate reflex) transients are shown in lower portion of figure.

caused by respiration; y is the output of the pacemaker and has a periodic solution. The maxima of y are considered to correspond to the times of firing of the pacemaker.

Comparison of the predicted and actual heart rate changes has been carried out successfully, showing a good correspondence for a wide variety of breathing modes.

Figure 1 shows a portion of a half-hour simulation record showing heart rate, simulated heart rate, and respiration for various modes of breathing. The simulated heart rate was computed by the analog computer and simultaneously recorded with the actual heart rate (*5*). The only signal entering the computer from the subject was the subject's respiration in the form of an electric signal proportional to thorax circumference. The actual and simulated heart rate are recorded above each portion of the respiration record. The record was taken with the subject in a resting state, supine; the subject was a 26-year-old male. Each ordinate represents the time between two consecutive heart beats, measuring from R to R peak of the QRS complex of the electrocardiogram. Thus a long line represents a slow heart rate, a short line a fast heart rate. The basic inspiratory and expiratory heart rate transients are shown in the lower parts of the figure.

Parameters of the differential equations represented by the computer remained unaltered during the course of the simulation. Note the correspondence between actual and simulated heart rates. Since the measure taken of respiration is the external circumference of the thorax, some amplitude dissimilarities between the stretch experienced by the organic receptor and our recording device is to be expected. Some nonlinearities in this regard are likely.

Note that a slight dissimilarity is actually theoretically required, since each cardiac cycle in the simulated circuit does not begin synchronously with the actual heart. Consequently, a deep inspiration, for example, does not necessarily begin at the same point in the cardiac cycle in the simulated circuit as in the real heart, thus causing a minor deviation in the transient. Some steady state changes in heart rate with extent of chest expansion are also sometimes found in addition to the transient changes described.

It may be concluded that in the unanesthetized human being, respiratory sinus arrhythmia (the heart rate changes caused by respiration) is initiated by stretch receptors located within the chest and is not primarily caused by hemodynamic factors or central influences. The paradoxical findings regarding the phasic relation between heart rate and respiration are resolved by showing that the heart rate waves observed are in fact superpositions of biphasic transients of definite shape and duration. As a result of the mathematical analysis, in terms of nonlinear differential equations, it is possible to predict the heart rate changes (both regular and irregular) due to respiration for any manner of breathing in the given subject.

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22 June 1959

Solid-Counting of Octadecane-1-H^3

Abstract. A solid sample of octadecane-1-H^3 was found to show a fairly good proportionality of the counting rate to the amount of the sample. Taking account of the synthetic process, nonvolatility, and spreadability of octadecane, this compound offers a possibility of being used as a standard sample for counting the radioactivity of tritium.

Many investigators have attempted to count the radioactivity of tritium, which emits extremely soft β-rays, by gas-phase (*1*) and liquid scintillation (*2*) counting. However, these methods require some special and expensive equipment and complicated procedures. Moreover, it seems inevitable that these methods should suffer from some difficulties—for example, memory effect for the former method and limited applicability for the latter—in performing the measurement. To avoid the memory effect, attempts were successfully made to perform the solid-counting of vegetable oil (*3*) and *p*-aminosalicylic acid (*4*), both tagged with tritium. A weakness of the use of these two substances, however, arises from limited applicability: The first must be synthesized by adding tritium as a gas to unsaturated oil; the second, by a gas-exposure method in which carrier-free tritium gas is used (*5*).

Because of these difficulties, it seems desirable to change a sample of organic compound tagged with tritium to a standard form through a common process such as

$$\text{H}^3\text{-tagged organic compound} \xrightarrow{\text{burn}} \text{H}^3_2\text{O} \longrightarrow \text{standard substance to be counted}$$

To practice good solid-counting, the final product should be (i) prepared easily and quantitatively from H^3_2O, (ii) nonvolatile at room temperature, and (iii) uniformly spreadable on a suitable surface. Octadecane, synthesized by the reaction of tritiated water and excess octadecyl magnesium bromide, satisfies the first two conditions, and, when it contains a small amount of amphipathic compound, it may also satisfy the third. Thus, this compound seems to be suitable for a standard sample to be counted.

In the present experiment, octadecane-1-H^3, synthesized by the above reaction and containing a small amount of octadecanol, was used. A portion of this substance was spread from benzene solution onto the bottom of a stainless steel pan (24.5 mm in diameter), and the radioactivity was determinated by using a 2π flow counter (Aloka, type DC-1001). Commercial propane was used as a flow gas (*6*).

Figure 1 shows a dependence of the counting rate upon the sample thickness. The calculation assumes uniform spreading of octadecane over the bottom of the pan, though this is not always valid. In spite of this rough assumption, the counting rate increased proportionally with the increase of the sample thickness, when the amount of the sample was less than that corresponding to the maximum range of β-rays. Within this region, the counting rate was reproducible for a given amount of the sample, irrespective of distribution of the sample over the bottom of the pan. Beyond this region,

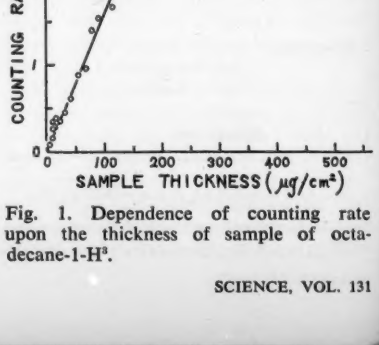

Fig. 1. Dependence of counting rate upon the thickness of sample of octadecane-1-H^3.

however, the counting rate was affected by several conditions, such as an uneven distribution and the surface roughness of samples.

Through all experiments, no memory effect was observed. A memory effect would hardly be anticipated from the low volatility of octadecane. The present results suggest an applicability of the solid-counting method to soft β-rays of tritium-tagged substances, if the sample thickness is chosen to be in a proportional region, as shown in Fig. 1.

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10 July 1959

Electron Transfer and Absorption Spectra of Complexes

Abstract. Occurrence of light saturation in the reaction of thionine (T) with Fe^{3+} suggests the existence of $T{\cdot}Fe^{3+}$ complexes practically indistinguishable by their absorption spectra from free thionine; photoreduction seems to occur by electron transfer in such complexes, delayed by more than 10^{-5} second after light absorption. Both phenomena must be of general significance.

It has been customary to use absorption spectra to decide whether two reagents in solution form a complex or not. It was assumed that the absorption spectrum of the complex must be different from that of its components, at least to the extent to which the spectrum of a dissolved molecule usually is affected by the solvent.

However, Watson (*1*) had to postulate the occurrence of phenylhydrazine complexes of chlorophyll to account for the effect of this compound on the fluorescence of chlorophyll; and yet no change in the absorption spectrum of chlorophyll could be noted upon the addition of small amounts of phenylhydrazine. Bannister (*2*) had to make a similar assumption in the case of chlorophyll and ascorbic acid to explain the kinetics of the photoreduction of chlorophyll by this compound. Weber (*3*) found that enzymatic removal of the nicotinamide nucleus from diphosphopyridine nucleotide does not affect the absorption spectrum; and the absorption spectrum of ethyl chlorophyllide was found, by Holt and Jacobs (*4*), to be practically identical with that of chlorophyll (phytyl chlorophyllide); so it was shown that even chemical bonding sometimes leaves the absorption spectrum practically unchanged.

One of us (S.A.) arrived at a similar conclusion in a systematic study of the kinetics of photoreduction of thionine (T) by ferrous ions. The phenomenon of light saturation, unusual in simple photochemical reactions in vitro, which he observed in concentrated ferrous solutions (10^{-3} mole/liter or more) was most easily explained by postulating, as the main or only photosensitive species, a $T{\cdot}Fe^{3+}$ complex with a finite velocity of formation in the dark (see reaction 1, where T_r stands for reduced thionine):

$$\overset{K}{\rightleftharpoons} \quad \overset{+h\nu}{\longrightarrow}$$

$$^1T + Fe^{3+} \rightleftharpoons {}^1T{\cdot}Fe^{3+} \longrightarrow {}^1T^*{\cdot}Fe^{3+} \rightarrow {}^3T{\cdot}Fe^{3+} \rightarrow T_r + Fe^{3+} \quad (1)$$

Light saturation is reached, in system I, when the rate of complex formation limits the rate of the photochemical reaction.

Yet, measurements of the absorption spectrum of thionine solutions in the presence of ferrous ions show no evidence of complexing. In fact, Hardwick (*5*), in a recent study of the same reaction, used this fact to exclude a complex mechanism and to treat the reactions as due to encounters of metastable thionine molecules with free ferrous ions. Schlag (*6*) also disregarded complex formation in his study of the thionine-iron reaction. Havemann and his co-workers (*7*), on the other hand, did inquire into the possible existence of complexes, confirmed their existence by measurements of the effect of Fe^{3+} ions on fluorescence, and assumed complexes to be the photosensitive species in the interpretation of kinetic data. They derived a value of $K = 30$ for the complex formation constant.

The kinetic data obtained in our laboratory, and presented in detail in a paper by Ainsworth (*8*), led to a somewhat higher complexing constant, $K = 200$.

In the present report we would like to point out the apparently widespread existence of dye complexes more or less completely indistinguishable from free dye molecules by their absorption spectra. In the case of the system $T + Fe^{3+}$ (as well as in that of the system chlorophyll + ascorbate), this behavior suggests that electron transfer can occur, in an excited complex, not as an immediate result of light absorption—in which case a new "electron-transfer" band could be expected to appear in the absorption spectrum (*9*)—but as a delayed effect. As suggested in reaction 1, the dye molecule in the excited complex may be first transferred into a metastable triplet state; this transfer is so effectively catalyzed by the paramagnetic Fe^{3+} ions as to quench fluorescence completely. An electron is transferred to the triplet dye from the associated Fe^{3+} ion after an average life-time of at least 10^{-5} second; this is indicated by the observation that the reaction is quenched by ferric ions [as well as by thionine molecules (see *10*)] in concentrations as low as 10^{-8} mole/liter. (Even resonance energy migration could not account for significant quenching of a *singlet* excited state by a quencher present in such low concentrations.) Another consequence of this mechanism is the probability of a primary back reaction within the complex; this may explain why the highest quantum yield of the $T + Fe^{3+}$ reaction that we were able to obtain was about 0.3.

The two conclusions—that spectroscopically unrecognizable complexes exist, and that delayed electron transfer occurs in such complexes after electronic excitation of one of the components—appear to be of some general interest.

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10 August 1959

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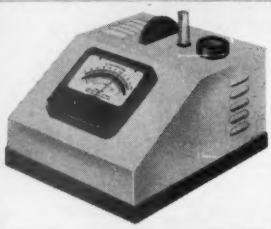

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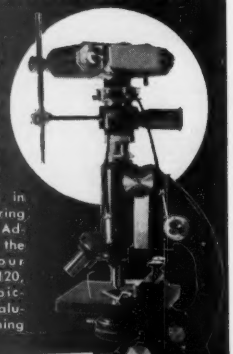

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Augmented sources of certified pure substances, a clearinghouse of information about the availability of such materials, and intensified research on all aspects of the purity problem are urgently needed by science and industry. This situation was revealed at a conference on Chemical Compounds of Certified High Purity, held 22 and 23 June at the National Academy of Sciences in Washington. Approximately 35 prominent scientists participated in the conference, which was sponsored jointly by the National Science Foundation and the National Academy of Sciences–National Research Council. Frederick D. Rossini of the Carnegie Institute of Technology was chairman of the conference and also of the five-man organizing committee appointed by academy president Detlev Bronk.

Highly purified compounds are necessary as standards of measurement, in the calibration of instruments, and in the definitive determination of physical and chemical properties requisite for the compilation of "critical tables" of enduring value. In fact, in any type of physical or chemical research where experimental results are sensitive to small amounts of impurity, the availability of pure compounds is imperative. The preparation of such materials simply has not kept pace with the tremendous strides made in recent years in instrumentation and experimental techniques of measurement.

Many major classes of inorganic, organic, and metallo-organic compounds should be made available, including biologically important classes of compounds. Discussion ranged widely over the diverse types of pure substances required—from monoisotopic elements such as oxygen-17 to complex proteins such as insulin, and from single crystals and semiconductor materials to more prosaic compounds. It was also revealed that new criteria for determining purity are needed by biochemists, chemists, and physicists. The educators present agreed that a great increase in the availability of pure compounds speeds graduate research but also results in a certain loss from the standpoint of teaching, which must be remedied.

At the conclusion of the conference recommendations were made for the establishment of a center of information on existing sources of chemical compounds of certified high purity and for the establishment of a permanent central technical organization with responsibility for the identification, preparation, further purification, and certification of pure chemical compounds. It was also recommended that the National Academy of Sciences–National Research Council, in cooperation with other national and international scientific groups, implement a program for improved communication among laboratories concerned with the pure-compounds problem and encourage research on all aspects of the purity of chemical compounds and on the analytical chemistry pertaining to this work.

A limited number of copies of a report on the conference has been prepared. These are available to persons concerned with the pure-compounds problem and may be requested from the Office of Critical Tables, National Academy of Sciences, 2101 Constitution Avenue, NW, Washington 25, D.C.

GUY WADDINGTON

National Academy of Sciences, Washington, D.C.

Forthcoming Events

February

25–27. Cell Physiology of Neoplasia (14th annual symp. on fundamental cancer research), Houston, Tex. (Editorial Office, Univ. of Texas M. D. Anderson Hospital, Texas Medical Center, Houston 25.)

26. Highway Geology, 11th annual symp., Tallahassee, Fla. (W. F. Tanner, Geology Dept., Florida State Univ., Tallahassee.)

28–5. American College of Allergists, Miami Beach, Fla. (E. Bauers, 2160 Rand Tower, Minneapolis 2, Minn.)

29–3. American College of Surgeons, Boston, Mass. (H. P. Saunders, 40 E. Erie St., Chicago, Ill.)

29–4. Pittsburgh Conf. on Analytical Chemistry and Applied Spectroscopy, Pittsburgh, Pa. (L. P. Melnich, U.S. Steel Corp., Monroeville, Pa.)

March

2–4. Low and Medium Energy Nuclear Physics, colloquium, Grenoble, France. (F. Netter, C.E.N., Saclay, BP. No. 2, Gif-sur-Yvette, Seine et Oise, France.)

3–5. American Acad. of Forensic Sciences, Chicago, Ill. (W. J. R. Camp, AAFS, 1853 W. Polk St., Chicago 12.)

4–6. National Wildlife Federation, Dallas, Tex. (C. H. Callison, 232 Carroll St., NW, Washington 12.)

6–13. American Otorhinologic Soc. for Plastic Surgery, Miami Beach, Fla. (J. G. Gilbert, 75 Barberry Lane, Roslyn Heights, N.Y.)

7–9. Wildlife Management Inst., Dallas, Tex. (C. R. Gutermuth, 709 Wire Bldg., Washington 5.)

7–11. American Soc. of Civil Engineers, New Orleans, La. (E. S. Kirkpatrick, ASCE, 33 W. 39 St., New York 18.)

10. Recent Developments in Poultry Nutrition (Assoc. of Vitamin Chemists), Chicago, Ill. (J. T. Sime, Director of Research, Evaporated Milk Assoc., 228 N. La Salle St., Chicago 1.)

10–11. Institute of the Aeronautical Sci-

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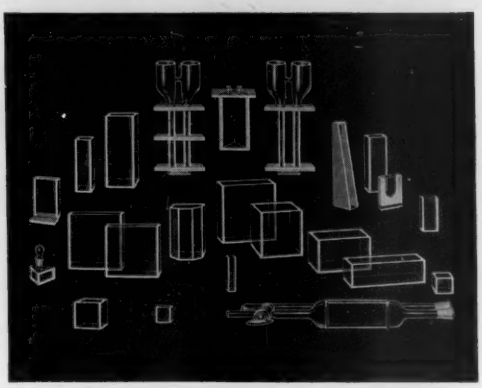

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Ibid, 20, 601 (58)

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14–16. American Railway Engineering Assoc., annual conv., Chicago, Ill. (N. D. Howard, AREA, 59 E. Van Buren St., Chicago 5.)

14–17. Positive Health of Older People, forum, Miami Beach, Fla. (A. Mallach, National Health Council, 1790 Broadway, New York 19.)

14–18. National Assoc. of Corrosion Engineers, 16th annual, Dallas, Tex. (W. A. Mapler, NACE, 18263 W. McNichols Rd., Detroit 19, Mich.)

15–16. American Broncho-Esophangological Assoc., Miami Beach, Fla. (F. J. Putney, 1712 Locust St., Philadelphia 3.)

15–21. Nondestructive Testing, 3rd intern. conf., Tokyo and Osaka, Japan. (S. Ishizaka, Scientific Attaché, Embassy of Japan, 2514 Massachusetts Ave., NW, Washington 8.)

17. Congress for Pharmacists, 2nd annual, Jamaica, N.Y. (Congress for Pharmacists, Public Relations Office, St. John's Univ., Jamaica 32.)

17–19. American Radium Soc., conf., San Juan, Puerto Rico. (ARS, 635 East Union, Pasadena, Calif.)

17–19. Blood Platelets, intern. symp. (by invitation only), Detroit, Mich. (Miss S. A. Johnson, Henry Ford Hospital, Detroit 2.)

17–20. International Assoc. for Dental Research, Chicago, Ill. (D. Y. Burrill, Northwestern Univ. Dental School, 311 E. Chicago Ave., Chicago 11.)

18–19. American Laryngological Assoc., Miami Beach, Fla. (L. Richards, Massachusetts Inst. of Technology, Cambridge.)

20–23. American Assoc. of Dental Schools, Chicago, Ill. (R. Sullen, 840 N. Lake Shore Drive, Chicago 11.)

20–26. American Cong. on Surveying and Mapping, Washington, D.C. (C. E. Palmer, American Soc. of Photogrammetry, 1515 Massachusetts Ave., NW, Washington 5.)

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21–24. American Acad. of General Practice, 12th annual, Philadelphia, Pa. (AAGP, Volker Blvd. at Brookside, Kansas City 12, Mo.)

21–24. Institute of Radio Engineers, natl. conv., New York, N.Y. (L. G. Cumming, IRE, 1 E. 79 St., New York 21.)

23–25. National Council on Alcoholism, annual, New York, N.Y. (M. Ross, American Psychiatric Assoc., 1700 18 St., NW, Washington 9.)

23–25. Optical Spectrometric Measurements of High Temperatures, symp., Chicago, Ill. (F. Brech, Laboratories for Applied Science, Univ. of Chicago, 6220 S. Drexel Ave., Chicago 37.)

24–25. Human Factors in Electronics, 1st annual symp. (IRE), New York, N.Y. (J. E. Karlin, Bell Telephone Laboratories, Murray Hill, N.J.)

24–26. American Assoc. for the History of Medicine, Charleston, S.C. (J. B. Blake, c/o Smithsonian Institution, Washington 25.)

24–26. Aviation Education, 4th natl. conf., Denver, Colo. (W. Kinkley, Superintendent of Schools, Aurora, Colo.)

26–27. American Psychosomatic Soc., 17th annual, Montreal, Canada. (E. D. Wittkower, APS, 265 Nassau Rd., Roosevelt, N.Y.)

28–31. Exploitation of Natural Animal Populations, symp., Durham, England. (E. D. Le Cren, British Ecological Soc., The Ferry House, Ambleside, Westmorland, England.)

29–31. American Power Conf., 22nd annual, Chicago, Ill. (R. A. Budenholzer, Mechanical Engineering Dept., Illinois Inst. of Technology, 3300 Federal St., Chicago 16.)

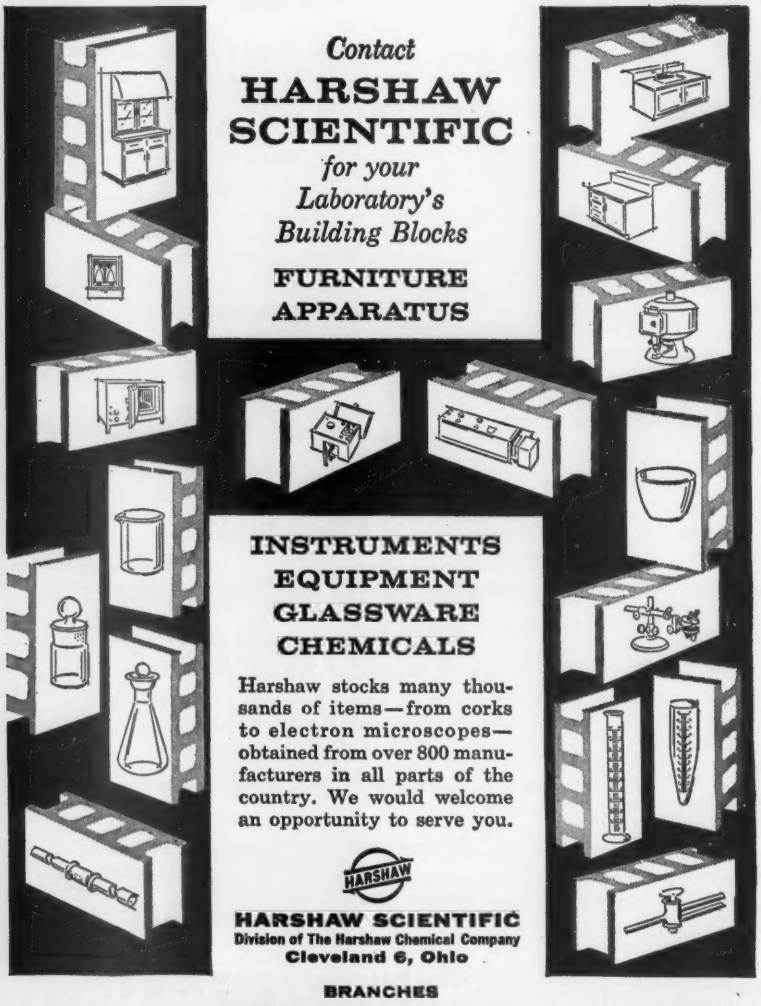
29–2. National Science Teachers Assoc., 8th annual conv., Kansas City, Mo. (Miss M. R. Broom, NSTA, National Education Assoc., 1201 16 St., NW, Washington 4.)

30–31. Adrenergic Mechanisms, Ciba Foundation symp. (by invitation only), London, England. (G. E. W. Wolstenholme, Ciba Foundation, 41 Portland Pl., London, W.1, England.)

31–1. Continuous Culture of Microorganisms, symp., London, England. (R. Elsworth, c/o Ministry of Supply, Microbiological Research Establishment, Porton, Salisbury, Wilts., England.)

31–2. American Gastroenterological Assoc., New Orleans, La. (W. Volwiler, Dept. of Medicine, Univ. of Washington, Seattle.)

(See issue of 15 January for comprehensive list)



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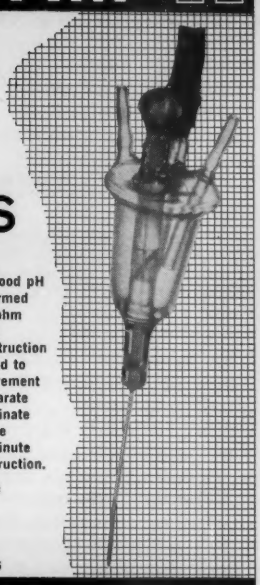

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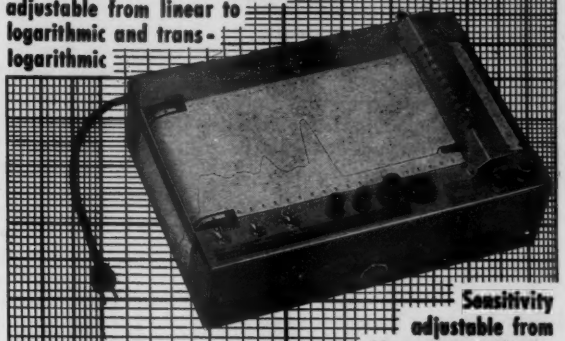

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Residence Address.....
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Age..... ☐ Single ☐ Married ☐ Male ☐ Female
Occupation.....
Location of Car (if different from residence address).....
Is car principally kept and used on a farm or ranch?.....

Yr.	Make	Model (Dlx., etc.)	Cyl.	Body Style	Purchase Date Mo. Yr.	☐ New ☐ Used

1. (a) Days per week car driven to work?..... One way distance is.....miles.
(b) Is car used in any occupation or business? (Excluding to and from work) ☐ Yes ☐ No

2. Additional male drivers under age 25 in household at present time:

Age	Relation	Married or Single	% of Use

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New Products

The information reported here is obtained from manufacturers and from other sources considered to be reliable. Neither Science *nor the writer assumes responsibility for the accuracy of the information. All inquiries concerning items listed should be addressed to the manufacturer. Include the department number in your inquiry.*

■ VACUUM SYSTEM is a mobile unit that will produce vacuum in the range 250 to 0.5 mm-Hg and hold within ±0.2 mm-Hg in an airtight system. The system uses a mechanical pump with free-air capacity of 58 lit./min. The pump runs continuously, evacuating a ballast tank connected to the rest of the system through a solenoid valve. The latter is controlled by a mercury regulator working through a relay. (Fisher Scientific Co., Dept. Sci292, 717 Forbes St., Pittsburgh 19, Pa.)

■ LIGHT SOURCE for high-speed photography is a spark-type point source. The source may be triggered with a 500-volt pulse of 2 μsec duration. Four models are available with energies at 20 kv of 2 to 20 joules and spark duration from 0.3 to 1 μsec. Source size ranges from 0.015 to 0.060 in. in diameter. The outer cylindrical case serves as a shield for radio frequencies. (Avco Corp., Dept. Sci334, 201 Lowell St., Wilmington, Mass.)

■ CATHODE-RAY-TUBE TRANSFER LENS provides a full-size image at object-to-image distance of 17.6 in. A 4½-in. diagonal format can be covered. Relative aperture ranges from *f*/2 to *f*/22. The lens is color-corrected over the range 4200 to 5200 A. A reflecting unit and a motorized adjustment of the lens iris are optional auxiliaries. Full-range operation of the iris by the latter requires less than 10 sec. (Perkin-Elmer Corp., Dept. Sci295, Norwalk, Conn.)

■ CHROMATOGRAM SCANNER for tritium, carbon-14, and sulfur-35 counts simultaneously both sides of one or more continuous strips up to 50 ft long. The entire strip is enclosed within the gas-filled scanner housing. Two facing gas-flow detectors accept collimated radiation from both sides of the strip and transmit total activity to a recorder. Ten scanning speeds are selectable. (Atomic Accessories Inc., Dept. Sci341, 244-02 Jamaica Ave., Bellerose 26, N.Y.)

■ GAUSSMETER is a direct-reading instrument for measurement of direction and magnitude of magnetic flux. Operation depends on the Hall effect: a thin wafer of high-purity indium arsenide with a temperature coefficient of 0.1 percent is used. The wafer element is 0.019 in. thick and 0.125 in. wide. The active area is a circle 0.0625 in. in diameter. Three ranges cover 0 to 300, 0 to 3000, and 0 to 30,000 gauss. The instrument will read d-c flux in the presence of a strong a-c field. Power supply is a built-in 4.5-volt battery. (F. W. Bell, Inc., Dept. Sci342, 1356 Norton Ave., Columbus 6, Ohio)

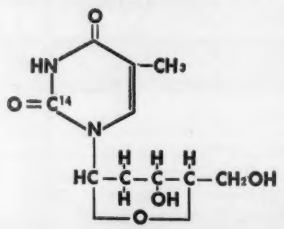
■ MONOCHROMATOR uses a 15,000-lines-in-plane grating as the dispersing element. Reciprocal dispersion is 70 A/mm. Slit widths are variable from 0 to 1 mm. Wavelength range is 200 to 1000 mμ. The instrument is reversible and can be mounted with slits vertical or horizontal. (Hilger and Watts, Dept. Sci323, 98 St. Pancras Way, Camden Rd., London N.W. 1, England)

■ METALLOGRAPH for microscopic study and photography of radioactive materials is remotely controlled. The instrument is built around the manufacturer's research metallograph and includes a control panel built into a shielding shell and mounting base that accepts whatever shielding material is desired. (Bausch and Lomb Optical Co., Dept. Sci336, Rochester 2, N.Y.)

JOSHUA STERN
National Bureau of Standards, Washington, D.C.

new england nuclear

THYMIDINE-2-C^{14}



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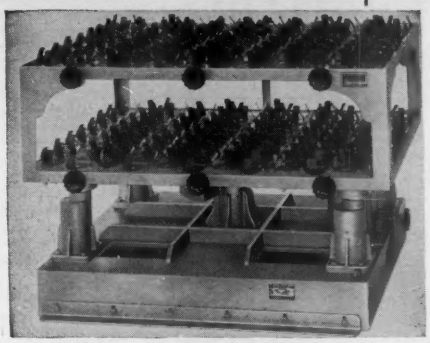

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Electron Microscopist, cytologist Ph.D. Desires staff teaching and research position university medical, zoology, or biology department. Grant support. Publications. Box 18, SCIENCE. 1/29

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POSITIONS WANTED

Biologist, Ph.D., 11 years' teaching experience. Numerous publications. Box 14, SCIENCE. 1/29; 2/5, 12

Teacher, Ph.D. (biochemistry), 44, male. Nine years of teaching undergraduate and graduate; 8 years of pharmaceutical research. Desires position in college emphasizing quality teaching. AAAS, ACS, Sigma Xi, publications. Available June 1960. Box 21, SCIENCE. X

POSITIONS OPEN

Biologist, Ph.D., to teach either cytogenetics, botanical sciences, or mammalian physiology in a Catholic university. Rank and salary open. Box 22, SCIENCE. 2/5, 12

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Plant Pathologists, Entomologists, Chemists— Ph.D. or equivalent, to supervise research projects in herbicides, fungicides, growth regulators, nematocides, and insecticides. Preferably with training or experience in entomology, plant pathology, organic chemistry, and plant physiology. Non-supervisory positions also available.

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Box 23, SCIENCE

(a) **Pharmacologist,** Ph.D., sufficient medical study for orientation; prefer teaching, research experience; prominent midwestern pharmaceutical concern; $10,000; university center. (b) **Biochemist;** Ph.D. to head blood chemistry laboratory, 400-bed university hospital; excellent southern location. (c) **Virologist-Tissue Culturist;** Ph.D. trained or experienced in isolation of viruses, cultivation cell cultures for research on problems related tumor viruses; new building, newly organized eastern research group in affiliation prominent medical center. (d) **Biochemist;** M.S. preferred to head section in well-departmentalized laboratory also serving other area hospitals as well as 400-bed general hospital; specialized medical staff; midwestern university center. (e) **Biochemist-Biologist;** interested molecular biology, experienced tissue culture techniques and/or virology; studies in nucleic acid metabolism, structure, function; university-affiliated research institute; Southwest. Woodward Medical Bureau, Ann Woodward, Director, 185 North Wabash, Chicago. X

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Box 24, SCIENCE

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University of Bristol. Applications are invited from qualified candidates of any nationality for **I.C.I. Research Fellowships** in chemistry, biological chemistry, engineering, pharmacology, physics, or related subjects, to which some appointments may be made to date from 1 October 1960, for a period of up to 3 years. The salary will be within the range £700–£1000 per annum. Applications (3 copies) stating age, qualifications and experience, publications, research work in progress, and an outline of the proposed field of research, with the names of two referees, should be received before **1 March 1960,** by the Registrar. (Candidates overseas may send one copy only by airmail.) X

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Prospective applicants should write for further information to Prof. H. Kleerekoper, Chairman, Department of Biology, Hamilton College, McMaster University, Hamilton, Ontario, Canada. Application forms both for scholarships and graduate study are obtainable from the Dean of Graduate Studies and must be returned to him normally by **1 March 1960,** accompanied by university transcript and letters of recommendation from two professors. 2/5, 12

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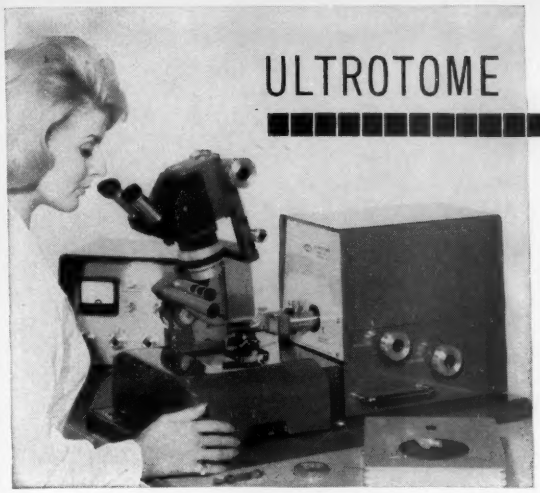

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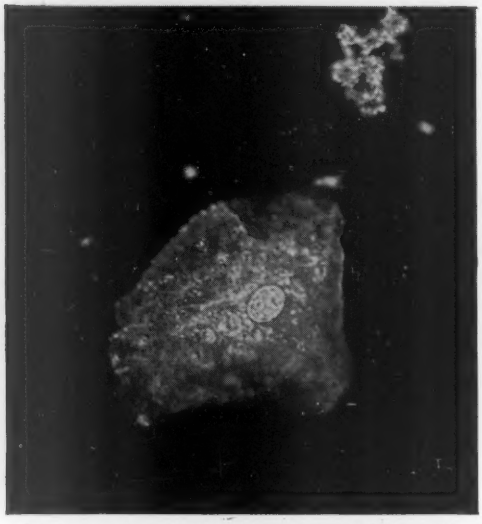

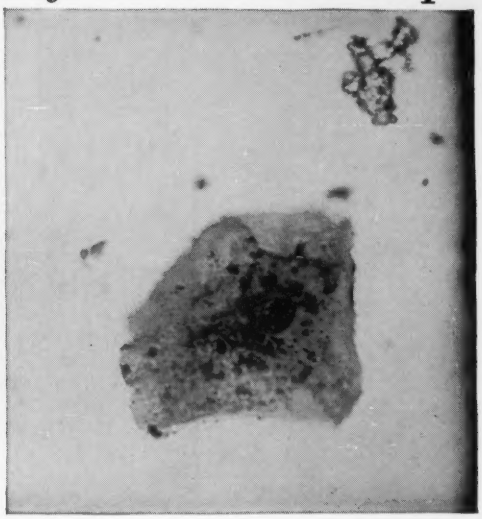

1. First, as shown in the photomicrograph* above, the microscope analyzer was rotated until the background was brought to extinction. Readings were taken directly from the analyzer scale. Averaged settings resulted in reading of 70.4°.

2. Next, the analyzer was rotated until the nucleus of the cell was brought to extinction. Averaged settings resulted in reading of 138.2°.

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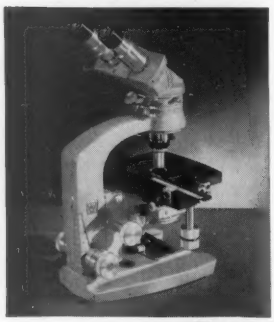

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